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# CONGENITAL NONSPHEROCYTIC HEMOLYTIC ANEMIA

## TWO NONFAMILIAL CASES WITH RED CELL SURVIVAL STUDIES

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DURING the past several years "nonspherocytic hemolytic anemia" has been separated from the previously identified groups of congenital hematological disorders. This hemolytic anemia is characterized by macrocytosis, basophilic stippling, hepatosplenomegaly, and jaundice. Typically the onset occurs in infancy and may simulate erythroblastosis fetalis. Using the available techniques of hematological analysis, this disorder can be differentiated from thalassemia, familial spherocytosis, the hemolytic diseases based on molecular abnormalities of hemoglobin, and acquired hemolytic disease. Evidence thus far presented suggests that it be considered as a clinical and pathogenic entity. Dacie and associates,[1] Kaplan and Zeulzer,[2a, b] and Crosby[3] have demonstrated by cross-transfusion studies that there exists an intrinsic defect of the red blood cells in this disease as in thalassemia, hemolytic anemia associated with abnormal hemoglobins, and spherocytic anemia. Thus far, however, the exact nature of this abnormality has not been elucidated. In most of the cases reported to date evidence of a genetic basis has been discovered.

It is the purpose of this report to present two additional cases of congenital, nonspherocytic hemolytic anemia. These patients have been shown to have a primary intracorpuscular defect as measured by red cell survival studies in the patients themselves and in normal persons. In reporting these cases we shall emphasize the clinical and laboratory features of the disease, pay particular attention to the factors which contribute to the hemolysis, and define the intracorpuscular defect on the basis of red cell survival, using red cells tagged with radioactive chromium.[51]

### CASE REPORTS

CASE 1.—V. T. (Univ. of Minn. No. 801835) (Fig. 1) is a 6-year-old female child who has been observed intermittently over her entire life at our clinic. Moderate jaundice was present

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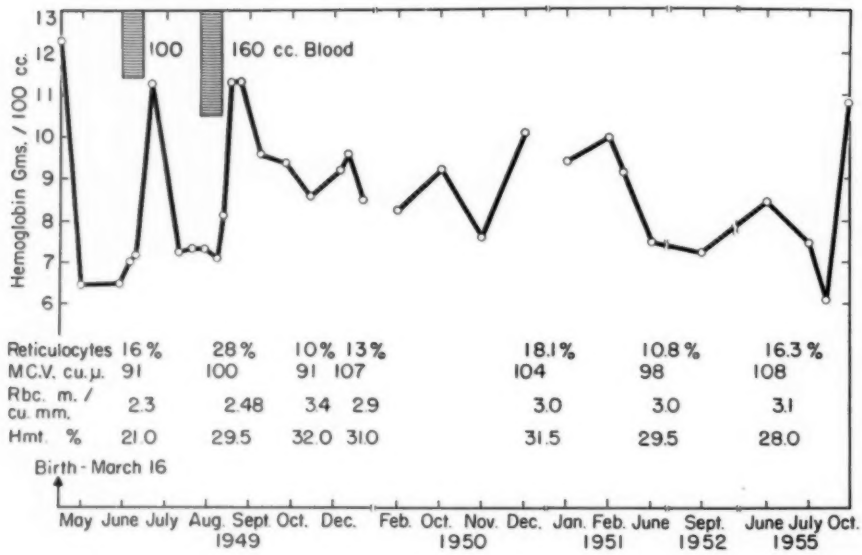
Hemoglobin Gms. / 100 cc.
13
12
11
10
9
8
7
6
100
160 cc. Blood
Reticulocytes 16 % 28 % 10 % 13 % 18.1 % 10.8 % 16.3 %
M.C.V. cu.μ. 91 100 91 107 104 98 108
Rbc. m. / cu. mm. 2.3 2.48 3.4 2.9 3.0 3.0 3.1
Hmt. % 21.0 29.5 32.0 31.0 31.5 29.5 28.0
Birth - March 16
May June July Aug. Sept. Oct. Dec. Feb. Oct. Nov. Dec. Jan. Feb. June Sept. June July Oct.
1949 1950 1951 1952 1955

Fig. 1.

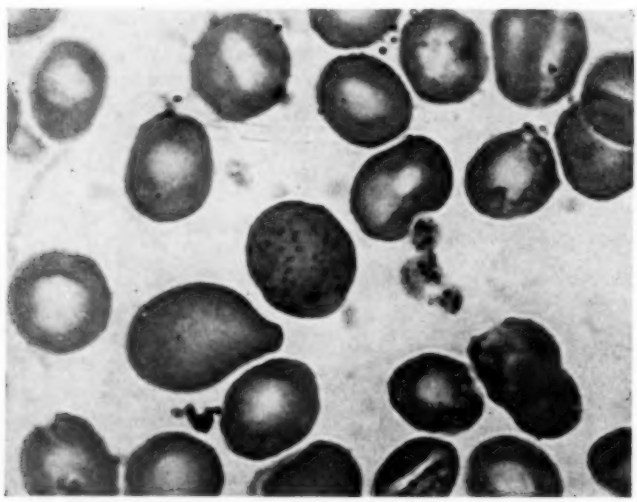

Fig. 2.

at 24 hours of age on March 14, 1949. The liver was palpable 4 cm. below the costal margin and the hemoglobin was 12.2 grams per 100 c.c. whole blood. The jaundice gradually disappeared and there were no further abnormalities during the immediate newborn period.

Increasing pallor became evident during the first four weeks of life. Iron therapy was begun after a hemoglobin of 6.6 grams per 100 c.c. was noted when the patient was 4 weeks old. This iron was taken as ferrous gluconate elixir 1 teaspoonful b.i.d. Despite adequate medication, a reticulocytosis of 14 per cent and hemoglobin of 7.0 grams were still present at 3 months of age and she was readmitted for study at the University of Minnesota Hospitals.

The infant, on physical examination, was nonicteric, well developed, and had a palpable liver 3 cm. below the right costal margin. A grade I apical systolic murmur was noted. Fluoroscopic study demonstrated cardiac enlargement thought by the roentgenologist to be compatible with severe anemia.

Measurements of hemoglobin, reticulocytes, and study of peripheral smears of the parents and siblings were normal. Review of the family history did not reveal any previous significant difficulties except that the mother had had a transient "anemia of pregnancy."

Laboratory examination demonstrated a hemoglobin of 7.2 grams per cent, a red blood cell count of 2.3 million per cubic millimeter, and a hematocrit of 21 per cent. The MCD was 8.0 meg. and the MCV was 91 cu. meg. Bone marrow and peripheral blood examination revealed a marked degree of basophilic stippling of the erythrocytes and normoblastic hyperplasia (Fig. 2.) The osmotic fragility was normal, beginning at 0.48 per cent and being complete at 0.32 per cent (the same as the control). Whole blood transfusions of 100 and 160 c.c. were given with no complications. Despite the anemia the infant continued to do well, with only an occasional upper respiratory infection.

At the age of 10 months, after continued therapy with ferrous iron, the patient was readmitted for study. The liver was palpable 3 cm. below the costal margin but the spleen was not palpable. The sclerae were clear. Laboratory examination revealed a fecal urobilinogen level of 240 E.U. per 100 Gm. This amount of fecal urobilinogen is considerably elevated for a 10-month-old infant with a hemoglobin of 8.0 grams per cent. The erythrocytic protoporphyrin was 105 gamma per 100 c.c. red blood cells (normal 27 to 38 gamma per cent). The urine coproporphyrin was 37.5 gamma per day (normal total for adults is 170 gamma per day). Test for porphobilinogen was negative. The basophilic stippling was again noted. The serum iron was 92 gamma per 100 red blood cells and the iron-binding capacity was 200 gamma per 100 red blood cells (normal 85 to 120 and 200 to 300, respectively). The direct and indirect Coombs tests were negative.

The patient continued to grow and develop normally despite a persistent anemia of 7 to 8 grams per cent, and reticulocytosis of 10 to 20 per cent. A mild cystitis was noted at 20 months, but after therapy with penicillin and sulfadiazine, urine cultures were sterile. An intravenous pyelogram showed a bifid left renal pelvis with minimal dilatation. No clinical difficulties have been related to this anomaly.

Clinically, although the hemolytic process continued unabated, the child adjusted well and got along without transfusions between the age of 10 months and 6 years. At 6 years of age she weighed 19 kilograms and was 114 centimeters tall (25 percentile according to the Iowa standards). The liver was palpable 3 cm. below the costal margin and the spleen was palpable at the left costal margin. There was a definite grade II systolic murmur in the pulmonic area which was considered to be "hemic" in origin by the pediatric cardiology staff. Her

hemoglobin was 8.2 grams per cent, reticulocytes 16.3 per cent.

The hemoglobin electrophoretic pattern was normal. On a Price-Jones curve many macrocytes were observed. The Coombs test was negative after trypsinization of the red blood cells. No urinary hemoglobin was found. Serum iron was 55 meg. per cent. The plasma hemoglobin was less than 12 mg. per cent. The fecal urobilinogen was 1,000 E.U. per 100 Gm. of stool. Coproporphyrin was 95 gamma per day. A reversal of the urinary coproporphyrin isomers was present. Type III isomer comprised 90 per cent of the total urinary coproporphyrins, whereas in normal children and adults type I is the predominant isomer. Other liver function tests, including cephalin cholesterol, thymol turbidity, and Bromsulphalein excretion were normal. Toxicological examination of the urine was negative for lead and arsenic. Bone marrow examination did not reveal any siderocytes or hemosiderin deposits.

A cross-transfusion study using radioactive $Cr^{51}$ was done. The patient's blood cells, tagged with $Cr^{51}$, when transfused into a normal subject showed a marked reduction in red cell survival time. Conversely, when normal blood cells tagged with $Cr^{51}$ by the same technique were transfused into the patient they showed a survival time only slightly shorter than that characteristic of normal cells in normal persons (Fig. 3).

A radioactive $Fe^{59}$ plasma clearance test was done. The plasma was incubated with 5 mc. of $Fe^{59}$ and then reinjected by vein. Normally the biological half-life time using this method is 90 minutes. The large amount of unsaturated iron-binding capacity assured us of no "tissue leakage." Immediately after injection, 2,010 counts per minute per cubic centimeter of plasma were present. Two hours later no radioactivity was detectable in the plasma. Although in this study no end-point was observed, the observation must be interpreted as evidence for an extremely rapid removal of iron-globulin complex from the circulation. In spite of intensive treatment with ferrous sulfate over a six-month period the hemoglobin remained

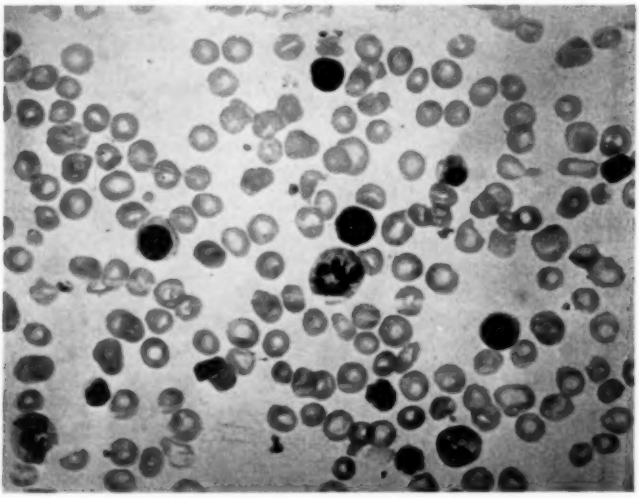

Fig. 3.

low (8.2 grams per cent) and reticulocytosis continued to be present (8.0 per cent).

CASE 2.—R. W. (Fig. 4). At 3 years of age this Chippewa Indian boy was referred to the University of Minnesota Hospitals for evaluation and therapy of hemolytic anemia.

Pallor, restlessness, and protuberant abdomen were first observed when he was 3 months old. His physician noted a severe anemia, with enlargement of both liver and spleen. The patient was treated with ferrous sulfate, vitamin $B_{12}$, liver extracts, and repeated blood transfusions without altering the course of the disease. Laboratory data revealed a persistent anemia of 6 to 8 grams hemoglobin per 100 cubic centimeters, normal saline fragility studies, negative Coombs test, and a normoblastemia of 18 per 100 white blood cells. Bone marrow biopsy was reported as showing "erythroid hyperplasia." Clinical jaundice was not evident, but the persistence of the anemia suggested the possibility of hemolytic disease and a splenectomy was performed at Red Lake Indian Hospital, Minnesota, when the child was 9 months of age. The spleen was noted to be twice normal size and microscopic sections demonstrated "normal splenic architecture with red cell engorgement of the pulp."

Despite the splenectomy and transfusions at intervals of ten weeks, the hemoglobin level could not be stabilized. The patient was then transferred to the University of Minnesota Hospitals.

Physical examination revealed hepatomegaly, carious stunted teeth, scleral icterus, and minimal "bossing" of the frontal bone. The weight was 21 kilograms and the height 96 centimeters. The following laboratory data were obtained on admission: red blood cells 1.6 million per cubic millimeters, hemoglobin 4.3 grams per 100 c.c., hematocrit 12 per cent, total white blood cell count 16,400 with 50 per cent neutrophils, 37 per cent lymphocytes, 6 per cent eosinophils, 6 per cent monocytes, and 1 per cent basophils. There were 25 normoblasts per 100 white blood cells (Fig. 5). Reticulocytes were 2.5 per cent, platelets 200,000 per cubic millimeter. The sedimentation rate was 90 mm. per hour (Westergren). His calculated red blood cell indices were MCV 83

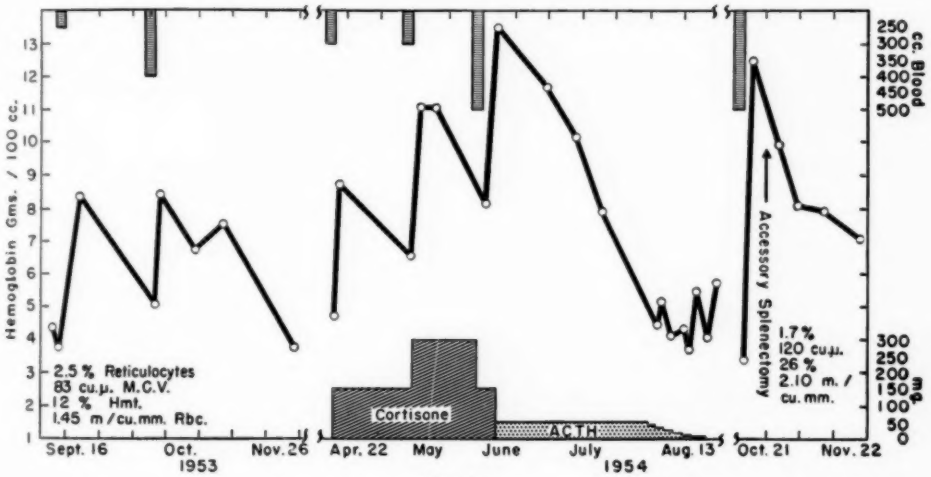


Fig. 4.

cu. meg., MCH 28 per cent, MCC 34 per cent, MCD 8.18 meg. The bilirubin was 1.3 mg. per cent total, of which 0.1 mg. per cent was the direct reaction of component. According to our standards this represents a slight increase in indirect reacting bilirubin. The fecal urobilinogen was 233 mg. per 100 Gm. The erythrocytic protoporphyrin and coproporphyrin were, respectively, 71 and 3.8 gamma per 100 c.c. red blood cells (upper limits for normal children 40 and 2.0 gamma per cent, respectively). The serum iron was 308 meg. per cent (upper limit of normal 120). The following blood tests gave values within the normal range: hemoglobin electrophoretic pattern, alkali resistant hemoglobin content, osmotic fragility, cold agglutination, direct and indirect Coombs test, and sickle cell preparation. Additional studies that were negative included: serological tests for syphilis, thymol and cephalin flocculation, BUN, total and esterified cholesterol, serum chloride, sodium, potassium, carbon dioxide combining power, C-reactive protein, antistreptolysin titer, and Mantoux 1:1,000 and 1:100 O.T. Similarly, no porphobilinogen hemosiderin or hemoglobin was found in the urine which contained a normal concentration of coproporphyrin (102 gamma per twenty-four hours). Isomer studies were not done.

Hematological examinations of the parents and six siblings did not reveal any similar disorder. No pathological red cells or increased reticulocytes were noted on peripheral smears. One sibling had an iron deficiency anemia which responded promptly to simple ferrous sulfate therapy.

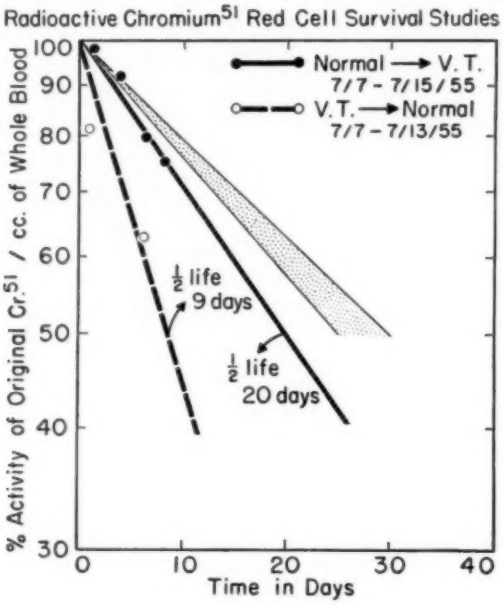


Fig. 5.

*Endamoeba histolytica* cysts and positive guaiac reactions were noted on repeated stool examinations. Proctoscopy added credence to the possibility of amebiasis because of the presence of a few pinpoint petechiae on the sigmoid mucosa. In addition, low-grade fever, leukocytosis, and the tender enlarged liver suggested that a therapeutic trial of antiamebic chemo-

therapy be given. Milibis (250 mg.) and Chloroquin (75 mg.) were used twice a day for six days. The child's temperature returned to normal and a second course of the same drugs was given for seventeen days. Subsequently repeated stool and proctoscopic examinations were all normal. The anemia, which was a chronic problem, was in no way affected by treatment of the amebiasis.

Thereafter, because he required 300 to 400 c.c. of whole blood every four weeks to maintain his hemoglobin and because we felt that acquired hemolytic anemia based on immunological mechanisms may rarely give rise to false negative results with the Coombs test, steroid therapy was tried. Cortisone initially in a dose of 150 mg. per day for four weeks, then 300 mg. per day for three weeks, and finally ACTH 50 mg. per day for six weeks were given. Despite the development of a marked "Cushing syndrome" and mild hypertension (140/90), the hemolytic process continued unabated.

Repeated red cell survival studies using radioactive $Cr^{51}$ were undertaken and definitely demarcated an intracorpuscular defect (Fig. 6). Finally, as in Case 1, the survival studies of normal red blood cells in this patient giving half-life values slightly shorter than was the case in normal persons, indicated that an extracorpuscular mechanism was contributing to the hemolysis. Consequently, an exploratory laparotomy was done in the hope of finding an accessory spleen, the removal of which we anticipated might ameliorate the hemolytic process. Indeed a large accessory spleen weighing 117 grams was found in the left upper quadrant in the bed of the spleen which had previously been removed. Microscopic study of the accessory spleen revealed only an increase in red pulp and large amounts of iron pigment in the perivascular areas. A

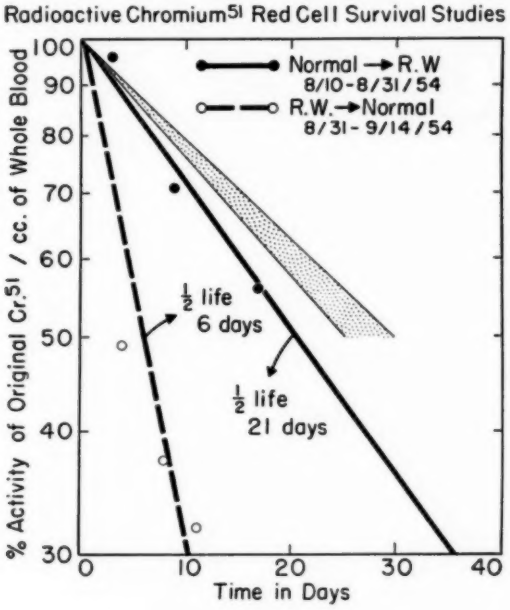


Fig. 6.

TABLE I. PIGMENT METABOLISM IN PATIENTS WITH CONGENITAL NONSPHEROCYTIC HEMOLYTIC ANEMIA

| | NORMAL | CASE 1 | | | | CASE 2 |
|---|---|---|---|---|---|---|
| | | 8-15-49 | 12-49 | 2-13-51 | 7-6-55 | |
| Urinary coproporphyrin (gamma/day) | 50-250 | 180 | 37.5 | 93.0 | 95.0 | 102.0 |
| *Type III isomers (per cent) | Less than 20 per cent | | 84.0% | 78.0% | | |
| Fecal urobilinogen (E. U./100 Gm.) | Normal hemoglobin approx. 200 | 128 | 240.0 | 400.0 | 1000.0 | 194.4 |
| Erythrocytic protoporphyrin (gamma per cent/100 c.c. RBC) | 27-32 | 120 | 105.0 | 86.0 | 114.0 | 71.0 |
| Erythrocytic coproporphyrin (gamma per cent/100 c.c. RBC) | 1 or less | | | 5.2 | 2.0 | 3.8 |
| Serum iron | 85-120 | | 92.0 | 63.0 | 55.0 | 308.0 |
| Total iron-binding capacity | 200-300 | | 200.0 | 265.0 | | |

*This is the normal value reported in adults in Dr. C. J. Watson's laboratory. However, Dr. Robert A. Aldrich in *American Journal of Medical Sciences*, December, 1955, states that the Type III isomer represents 90 per cent of the total urinary coproporphyrin excretion in normal children.

liver biopsy done at the time revealed "marked hemosiderosis and minimal myeloid metaplasia."

Despite a temporary decrease in the requirement for transfusion following splenectomy the hemolytic process quickly returned to its previous state. The child was finally discharged for care in his local community where he requires transfusions of 200 c.c. of whole blood every four to six weeks to keep his hemoglobin above 6 grams.

### CHROMIUM$^{51}$ RED CELL SURVIVAL STUDIES

Labeled red cells were prepared with radioactive chromate (Abbott) by the previously described ascorbic acid technique.[4] The survival of these cells both in the patient and in normal volunteers was followed by sampling at intervals. The percentage change in radioactivity of the red cells of whole blood was measured after correction for plasma activity and the physical decay of the isotope. Previous control studies have shown that in the normal individual, a reproducible half-life for red cells labeled in this manner is approximately 25 to 30 days.

Both patients had their red cells transfused into a normal recipient. The half-life of the radioactive $Cr^{51}$ was 9 and 6 days, respectively. Thus this remarkably shortened life cycle definitely indicated the presence of an intracorpuscular defect.

Conversely, normal red cells when transfused into our patients exhibited a survival approaching the average normal value. The half-life values of the normal cells in the two patients were, however, shorter than the lowest normal values. Therefore, we were forced to conclude that both patients presented evidence of an extracorpuscular hemolytic factor as well as the intracorpuscular defect. That such was the case was indicated by the temporary abatement of the hemolysis in Case 2 following removal of his accessory spleen. These results are reminiful of those of Lichtman and associates[5] and Smith and co-workers[6] who demonstrated that continued hemolysis in thalassemia major will produce a "hypersplenic" extracorpuscular abnormality contributing to the hemolytic process. In this light, the slight shortening of half-life of the

TABLE II. CHARACTERISTICS OF RED BLOOD CELLS IN PATIENTS WITH CONGENITAL NONSPHEROCYTIC HEMOLYTIC ANEMIA

| AUTHOR | CASE | MCV CU. MCG. | MACROCYTOSIS | RETICULOCYTES | MCD | STIPPLED CELLS |
|---|---|---|---|---|---|---|
| Holliday | | | | | | |
| | 1 | 99-125 | + | 4.5-19 | 7.9-8.9 | 0.4-9% |
| | 2 | 113 | + | 9.0-10 | – | Occas. |
| | 3 | 103-105 | + | 3.4-7.8 | 8.0 | Freq. |
| | 4 | Normal Hb.84 | Normal | 24 | 6.9 | |
| Zeulzer | | | | | | |
| | 3 | 106 | – | 25% | – | |
| | 1 | 100 | | 5-10 | | |
| | 2 | 115 | | 4-9 | | |
| | 3 | 130 | | 4-10 | | |
| Motulsky | | | | | | |
| | 1 | 110* | | 17.0 | | |
| | 3 | 90 | | 9.5 | | |
| | 4 | 95 | | 15.0 | | |
| Watson | | 104 | | 17.6 | | Basophilic stippling 10.87 |
| Crosby | | | | | | |
| | 1 | 105 | | 7.6 | | |
| | 2 | 103* | | 2.0 | | |
| Haden | | | | | | |
| | 1 | 1.29 vol. index. | | | 8.1 | – |
| | 2 | 1.15-1.07 | | | 8.2-7.9 | 45% |
| Dacie | | | | | | |
| | 1 | 113-120* | + | 50-70 | 8.7 meg. | + |
| | 2 | 114 | + | 14-28 | | + |
| | 3 | 102 | – | 4 | | + |
| | 4 | 118-125* | + | 55 | | + |
| Our cases | | | | | | |
| | 1 | 91-107 | + | 8-289 | 7.2 | Basophilic stippling |
| | 2 | 83-120* | + | 2.5-1.7 | 8.18 | – |

*Postsplenectomy values.

normal cells transfused into our two patients is not surprising.

Recorded in Table II is a summary of the cell indices characteristic of our patients and some of the cases presented in the literature. It may be seen from this table that the macrocytosis observed in our cases as revealed by MCV, MCD, and morphological observation is a common feature of this disease.

## DISCUSSION

The two case reports cited here must be classified with the group designated as nonspheroeytic hemolytic anemia. In both children the disease began in infancy and was due to moderate or severe hemolytic process. In both instances the laboratory features ruled out thalassemia, sickle cell disease, and acquired hemolytic anemia. The lack of a hereditary pattern, although unusual, has also been noted by Watson and Feinberg[8] and others.[1] Radioactive $Cr^{51}$ red cell survival studies established the existence of an intracorpuscular defect as the basis for the hemolytic disorder. However, evidence was obtained that in these patients as in others whose hemolytic disease is due primarily to an abnormality of the red blood corpuscles, extracorpuscular

factors may contribute to the total hemolytic process. Perhaps the macrocytosis noted in our study requires comment. Certainly it is not unique to our cases. Haden[9] and Holliday[10] have made pointed notation of this feature in other cases. Macrocytosis and increased mean corpuscular volume greater than 100 cu. meg. has been noted in each of the clinically affected cases of nonspherocytic hemolytic anemia. Occasionally reports of extremely large cell volumes ranging up to 130 cu. meg. have been noted. Lipton and associates[11] did have two cases with normal MCV. However, neither was established as an intracorpuscular defect by survival studies. Certainly, because of the relatively large size of immature red cells and the presence of reticulocytosis in our cases we cannot be certain that the macrocytosis was not a function of the immaturity of some of the cells in the peripheral blood. Wintrobe[12] has shown that the reticulocytosis associated with response of pernicious anemia to treatment results in an increased MCV. Theoretic calculations were offered to show that an increase in reticulocytosis of 6 per cent would be associated with a rise in MCV from 106 to 116 cu. meg. in pernicious anemia. It must be pointed out, however, that although a correlation between macrocytosis and reticulocytosis exists, the relationship in these patients is not good. In the cases of nonspherocytic hemolytic anemia listed in Table II and those reported here, it may be observed that the MCV be exceptionally high when reticulocyte percentages are relatively low. Regardless of its basis, macrocytosis is a clinical feature characteristic of nonspherocytic hemolytic anemia, and may in some way be associated with the intracorpuscular defect demonstrated to exist in these cases.

Because of the observation of basophilic stippling together with apparent reversal of the coproporphyrin isomers in our Case 1, heavy metal intoxication was considered. No evidence for intoxication could be found and the isomeric reversal remains an enigma (see footnote, Table I). Crosby's original patient had elevated urinary coproporphyrin almost two times the normal value. Unfortunately, in this latter case as in our Case 2 and others in the literature, the isomer ratio of the coproporphyrins was not studied. Such studies should be carried out in future investigations of this syndrome. In spite of the apparently normal liver function revealed in the study of our cases, it is conceivable that a defect of hepatic metabolism might occur which could result in macrocytosis, abnormal coproporphyrin excretion, and the formation of red blood cells excessively vulnerable to normal hemolytic processes within the body. Future studies of the porphyrin metabolism in this interesting hemolytic disease seem to be indicated.

The presence of increased fecal urobilinogen, reticulocytosis, and abnormal red cell survival studies were ample evidence for the presence of a continued hemolysis in these patients. In our Case 1, however, low serum iron and increased erythrocytic protoporphyrin were noted. Kaplan and Zeulzer[2a] similarly noted serum irons in 30 to 50 gamma range in his original three cases. Crosby[3] has also commented upon the paradoxical lack of siderocytes and normal serum iron in his patients. The punctate basophilic stippling in the erythrocytes has been

shown not to be iron in Case 1 and in others.[8] These observations are characteristic of a "chemical iron deficiency" despite the apparent and documented excessive hemolysis. In these cases the reticuloendothelial system must retain iron deposits in a particularly insoluble form. Such a "hemosiderin complex" conceivably could completely remove from the "metabolic pool" a disproportionate share of iron and thus render the total system "iron deficient." Such an hypothesis deserves further investigation.

In Case 1 a study of the capacity of the body to clear iron tagged with radioactive iron[59] was done. Complete disappearance from the plasma of the radioactivity as early as two hours after injection was noted. Crosby[3] and others[6] likewise have noted such rapid clearance values to be characteristic of their patients. The accelerated rate of removal of this tagged iron globulin complex reflects increased utilization by the hyperplastic erythroid system.

## SUMMARY

1. Two case reports of a congenital hemolytic anemia characterized by macrocytosis and basophilic stippling, neonatal jaundice, and hepatosplenomegaly are reported. The onset at birth and the continuing hemolytic disease have been described.

2. Employing survival techniques using red cells tagged with $Cr^{51}$ and cross-transfusion studies between diseased and hematologically normal persons established the essential corpuscular nature of this hemolytic disease.

3. Study of our cases and survey of the literature reveal that macrocytosis is a common feature of this disease.

4. Evidence that extracorpuscular factors may contribute to the hemolytic process in patients with this disease is presented.

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# HOW MUCH BED REST IS NECESSARY FOR CHILDREN WITH FEVER?

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SINCE you have fever, you should rest in bed for several days." This is the time-honored advice often given by physicians to their patients. This advice may be suitable for adults, but when we prescribe rest in bed for young children, we often run into difficulties. Some well-behaved children will stay in bed, but many children are so full of vitality, even when running fever, that they will not remain in bed. Others would remain in bed if they had better parental control, but this is often lacking. Some intelligent mothers have remarked, "When I keep him in his bed, he jumps and cries continually. It seems to me he would exert himself less if I let him play in the house."

Reluctantly, we have often been forced to accept this up-and-about situation that seemed undesirable and hazardous, especially when the child had a high temperature. Yet as time went by, a distinct impression began to form that the children with a high temperature who were up and about seemed to get well just as quickly as the better-controlled children who stayed in bed. Certainly, they had a better time, and the mother was happier with no trays to prepare and without the problem of keeping the child entertained.

Address: 202 Grape St.

This presented a practical question. How much bed rest is necessary for the child with a fever? If it is necessary, how enforce it? If not necessary, why advise it? Has any controlled study been made of this problem? Is "rest in bed" actually helpful or is it only another medical tradition?

In searching through the literature, no study could be found dealing with this specific problem. Two statements were found that were suggestive. English and Pearson said, "It is better to err on the side of allowing him [the ill child] to be a little too active than too inactive." Mitchell and Nelson in their textbook on pediatrics state, "Rest is perhaps nature's most efficient tool for repairing the ravages of disease, yet we know all too little of its quantitative administration. . . . One may err on the over side as well as on the under side. . . . Oftentimes, paradoxical as it may seem, physical activity is reduced by permitting greater latitude of movement. Who has not observed the restless, unhappy child confined to bed when his physical energies demanded an outlet? . . . At times, the child must be permitted extra privileges out of bed in order to lessen his physical activity. In many instances such restlessness may, of course, be an indication that the

child's activity is being unnecessarily and unwisely restricted."

In order to obtain specific information on the value of rest in bed for children with fever, a controlled study was made of 1,082 children over a two-year period (Nov. 9, 1953, to Nov. 9, 1955). These children were seen by me in private practice, in the office, or in the home. Hospital cases were not included. The study was conducted in a progressive midwestern city of 60,000 population, containing three colleges with an economic level considered above the average. Most of the mothers had thermometers and knew how to take temperatures orally or rectally.

## PLAN OF STUDY

The plan was to form two groups of pediatric patients who had fever: one group to remain in bed for at least three days, the other group to be up and about freely during their illness. These were not selected cases, but if the child was of runabout age and had fever I would ask the mother, "How is your child about staying in bed three days while he is ill, will he, or won't he?" I always attempted to ask this question in a noncommittal manner to encourage a frank answer. With few exceptions, her answer determined which group her child was to join. In either case temperatures were to be taken each afternoon at 4:30 P.M., and I was to contact her by telephone for a progress report and temperature readings. The 4:30 P.M. temperature was selected since it came before the evening meal, and at a time when the temperature would be at its higher levels. It was further a convenient time of the day to hold a "telephone session" at the end of the office day.

The mothers were instructed to take the temperature only once or twice a day, and not to give aspirin until they had actually found the temperature high. In this way we were able to record accurate temperature readings not influenced by aspirin. In those children who were to remain in bed for three days, specific inquiry was made as to whether the child had actually remained in bed for the full time. A good many children remained in bed for only one or two days, refusing to stay in bed any longer. Records on these children were discarded, as our aim was to have a group for comparison that actually remained in bed for three days. The mothers did not know that this study was being conducted.

Most of the children had been ill "for only a day or two" before being brought to the office. Temperature readings had not been taken with enough regularity to make tabulation worth while.

## COMPARISON OF GROUPS

During the two-year study, we have temperature records on 1,082 ill children. Of these, 471 remained in bed for three days while 611 were up and about in the house. Medications, diet, and other instructions were the same

TABLE I. COMPARISON OF TWO GROUPS IN REGARD TO SEX AND COLOR

| 1,082 CHILDREN WITH FEVER | | 471 CHILDREN IN BED 3 DAYS (PER CENT) | 611 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|---|
| Males | 552 | 46.2 | 54.5 |
| Females | 530 | 53.8 | 45.5 |
| Whites | 1,065 | 98.1 | 98.6 |
| Negro | 15 | 1.7 | 1.1 |
| Mexican | 2 | 0.2 | 0.3 |

for each group, the only variable factor being that one group was in bed for three days, while the other was up and about (Tables I, II, and III).

TABLE II. COMPARISON OF TWO GROUPS IN REGARD TO AGES

| 1,082 CHILDREN | | 471 CHILDREN IN BED 3 DAYS (PER CENT) | 611 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|---|
| Aged 1 through 5 yr. | 687 | 51.6 | 72.6 |
| Aged 6 through 10 yr. | 331 | 39.3 | 23.9 |
| Aged 11 through 15 yr. | 64 | 9.1 | 3.4 |

TABLE III. COMPARISON OF TWO GROUPS IN REGARD TO TIME OF YEAR THEY WERE ILL

| | 471 CHILDREN IN BED 3 DAYS (PER CENT) | 611 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|
| 1st 3 mo. | 21.7 | 15.6 |
| 2nd 3 mo. | 14.6 | 15.0 |
| 3rd 3 mo. | 10.0 | 13.6 |
| 4th 3 mo. | 7.0 | 6.9 |
| 5th 3 mo. | 14.2 | 17.2 |
| 6th 3 mo. | 13.7 | 13.2 |
| 7th 3 mo. | 12.3 | 13.1 |
| 8th 3 mo. | 6.5 | 5.4 |

As wave after wave of respiratory and other illnesses went through the pediatric population, there were comparative percentages in each group (Table IV).

Were the two groups comparable in regard to the medications used? Usually, a single medication was selected and given in full therapeutic dosage for three or four days. Then if the child seemed well no further medication was given. Since this is not a report on response to specific medications, code names will be used for the medications (Table V).

Over 80 per cent of the children in each group were given medications "A" and/or "B."

*Summary of Comparisons.*—The two groups are similar in respect to sex, color, ages, time of illness, and medications used. Only small variations are present.

### TEMPERATURE COMPARISON

We come now to the more interesting part of the study: a comparison of the temperatures of the children in the two groups. In looking at the groups as a whole, all ages, and all types of illnesses, did any marked difference occur in the two groups in the return of the temperatures to normal?

The records on the 20.4 per cent in each group who were still running fever on the fourth day were care-

TABLE IV. COMPARISON OF TWO GROUPS IN REGARD TO TYPES OF ILLNESSES

| | 471 CHILDREN IN BED 3 DAYS (PER CENT) | 611 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|
| Illnesses involving respiratory tract | 77.5 | 81.3 |
| Gastrointestinal illnesses | 5.5 | 2.4 |
| Contagious childhood diseases | 4.6 | 5.2 |
| Miscellaneous illnesses | 2.9 | 2.8 |
| No diagnosis | 9.5 | 8.3 |

TABLE V. COMPARISON OF THE TWO GROUPS IN REGARD TO MEDICATIONS

| | 471 CHILDREN IN BED 3 DAYS (PER CENT) | 611 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|
| Medication "A" | 65.1 | 61.3 |
| Medication "B" | 14.6 | 16.0 |
| Medications "A" and "B" | 6.1 | 3.7 |
| Other medications | 14.2 | 19.0 |

fully reviewed. Nearly all in each group were free from fever by the sixth day. Two in each group developed an otitis media. There were no other serious complications. No cases of acute nephritis or rheumatic fever were found in either group. There were no deaths.

ing to remain in bed (105 to 51). The fevers subsided at about the same rate in both groups.

Having considered the group of children as a whole, we next studied the groups according to the specific types of illnesses. There were fourteen children who had scarlet fever. Most

TABLE VI. COMPARISON OF THE TEMPERATURES OF A GROUP OF ILL CHILDREN WHO STAYED IN BED THREE DAYS WITH A GROUP WHO WERE UP AND ABOUT

| 1,082 CHILDREN WITH FEVER | 471 CHILDREN IN BED 3 DAYS (PER CENT) | 611 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|
| Temperature normal by 2nd day | 42.0 | 45.3 |
| Temperature normal by 3rd day | 27.1 | 23.5 |
| Temperature normal by 4th day | 10.4 | 10.6 |
| Temperature not normal by 4th day | 20.4 | 20.4 |

TABLE VII. COMPARISON OF THE TEMPERATURE RECORDS OF CHILDREN WITH MODERATELY HIGH FEVER, ALL AGES, ALL TYPES OF ILLNESS, ONE GROUP AT REST IN BED, THE OTHER UP AND ABOUT

| 471 CHILDREN WITH TEMPERATURES OF 101 TO 102.8° F. ORALLY (OR 102° TO 103.8° F. RECTALLY) | 219 CHILDREN IN BED 3 DAYS (PER CENT) | 252 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|
| Temperature normal by 2nd day | 45.2 | 45.2 |
| Temperature normal by 3rd day | 28.3 | 28.1 |
| Temperature normal by 4th day | 14.1 | 13.1 |
| Temperature not normal by 4th day | 12.3 | 13.5 |

TABLE VIII. COMPARISON OF THE TEMPERATURE RECORDS OF CHILDREN WITH HIGH FEVER, ALL AGES, ALL TYPES OF ILLNESS, ONE GROUP AT REST IN BED, THE OTHER GROUP UP AND ABOUT

| 156 CHILDREN WITH TEMPERATURES OF 103° F. AND OVER, ORALLY (OR 104° F. AND OVER, RECTALLY) | 105 CHILDREN IN BED 3 DAYS (PER CENT) | 51 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|
| Temperature normal by 2nd day | 47.6 | 50.9 |
| Temperature normal by 3rd day | 30.5 | 19.6 |
| Temperature normal by 4th day | 10.5 | 19.6 |
| Temperature not normal by 4th day | 11.4 | 9.8 |

Since children who have only one or two degrees of fever might have a normal temperature in a day or two, regardless of rest or activity, we reviewed the records of those who had moderately high and high temperatures (Tables VII and VIII).

When the illnesses were accompanied by the higher temperatures, a greater number of children were willhad high fever when first seen. All were treated with penicillin.

An examination of the urine of each child was made three weeks after the onset of illness. Nephritis or other complications did not occur in any of the fourteen children.

Among the 1,082 children, illnesses involving the respiratory tract ranked first (77 per cent for those in bed, 81

TABLE IX. COMPARISON OF THE TEMPERATURE RECORDS OF FOURTEEN CHILDREN WITH SCARLET FEVER

| SCARLET FEVER, 14 CHILDREN | 5 CHILDREN IN BED 3 DAYS | 9 CHILDREN UP AND ABOUT |
|---|---|---|
| Temperature normal by 2nd day | 3 | 5 |
| Temperature normal by 3rd day | 0 | 1 |
| Temperature normal by 4th day | 1 | 2 |
| Temperature not normal by 4th day | 1 | 1 |

TABLE X. COMPARISON OF THE TEMPERATURE RECORDS OF CHILDREN WITH ACUTE TONSILLITIS, OR ACUTE PHARYNGITIS, WITH TEMPERATURES OF 102° F. AND OVER ORALLY (OR 103° F. AND OVER RECTALLY)

| 201 CHILDREN | 116 CHILDREN IN BED 3 DAYS (PER CENT) | 85 CHILDREN UP AND ABOUT (PER CENT) |
|---|---|---|
| Temperature normal by 2nd day | 45.7 | 45.9 |
| Temperature normal by 3rd day | 29.3 | 25.9 |
| Temperature normal by 4th day | 11.2 | 14.1 |
| Temperature not normal by 4th day | 13.8 | 14.1 |
| Medications used in this group | | |
| Medication "A" | 75.8 | 68.2 |
| Medication "B" | 12.9 | 18.8 |
| Medications "A" and "B" | 5.2 | 2.3 |
| Other medications | 6.1 | 10.6 |

TABLE XI. COMPARISON OF THE TEMPERATURE RECORDS OF CHILDREN WITH ACUTE BRONCHITIS AND PNEUMONITIS, WITH TEMPERATURES OF 102° F. AND OVER ORALLY (OR 103° F. AND OVER RECTALLY)

| 65 CHILDREN | 39 CHILDREN IN BED 3 DAYS | 26 CHILDREN UP AND ABOUT |
|---|---|---|
| Temperature normal by 2nd day | 16 | 11 |
| Temperature normal by 3rd day | 15 | 6 |
| Temperature normal by 4th day | 5 | 4 |
| Temperature not normal by 4th day | 3 | 5 |
| Treated with medication "A" | 26 | 15 |
| Treated with medication "B" | 5 | 6 |
| Treated with medications "A" and "B" | 7 | 2 |
| Treated with other medications | 1 | 3 |

per cent for those up and about). Let us look at the records of those with infections of the upper respiratory tract, noting only those who had the higher temperatures.

There were sixty-five children in the respiratory group who were more seriously ill with acute bronchitis and pneumonitis, accompanied by high fever (Table XI).

In this small series, the fever of those who remained in bed subsided a little better than those who were up and about. Of those in bed, thirty-six of thirty-nine were normal by the fourth day, while in the up-and-about group, twenty-one of twenty-six were normal by the fourth day.

## DISCUSSION

It should be emphasized that this study did not include the more severe illnesses such as rheumatic fever, typhoid fever, and endocarditis. No hospital cases are included.

This study does seem to indicate that in the "ordinary" or "self-limited" illnesses of children treated in the office or the home, and which form the vast bulk of the practitioner's load, bed rest is not a decisive factor in favoring the return of the temperature to normal. Such children may rest as they desire, and may play quietly in the house. This will avoid penalizing obedient children with unnecessary confinement to bed, and will make life happier for the child and the mother. Though we may be guided by this general principle, we must still individualize our advice to the needs of each patient.

SUMMARY

In a controlled study of 1,082 ill children with fever, bed rest was not a decisive factor in favoring a return of the temperature to normal.

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*Witchcraft!*

On March 28, 1693 between 4 and 5 A.M. God gave to my Wife, a safe Deliverance of a *Son*. It was a child of a most *comely* and hearty Look, and all my Friends entertained his Birth, with very singular Expressions of Satisfaction. But the Child was attended with a very strange Disaster; for it had such an Obstruction in the *Bowels*, as utterly hindred the Passage of its Ordure from it. Wee used all the Methods that could bee devised for its ease; but Nothing wee did could save the Child from *Death*. It languished, in its Agonies till Saturday, April 1. about 10 h P.M. and so dy'd, unbaptised. . . .

When the Body of the Child was opened, wee found, that the lower End of the *Rectum Intestinum*, instead of being *Musculous*, as it should have been, was *Membranous*, and altogether closed up. I had great Reason to suspect a *Witchcraft*, in this praeternatural Accident; because my Wife, a few weeks before her Deliverance, was affrighted with an horrible Spectre, in our Porch, which Fright caused her Bowels to turn within her; and the Spectres which both before and after, tormented a young Woman in our Neighborhood, brag'd of their giving my Wife that Fright in hopes, they said, of doing Mischief unto her *Infant* at least, if not unto the Mother: and besides all this, the Child was no sooner born, but a suspected Woman sent unto my Father, a Letter full of railing against myself, wherein shee told him, *Hee little knew what might quickly befall some of his Posterity.*

—Diary of Cotton Mather.

# AMINOPHYLLINE (THEOPHYLLINE ETHYLENEDIAMINE) POISONING IN CHILDREN

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POISONING due to the oral or rectal administration of theophylline in ethylenediamine (aminophylline) has been infrequently reported since the drug first came into general use about 1936. Death associated with the enteral use of aminophylline was first reported by Gardner and associates[1] in 1950. They described the case of a 2-year-old female who ingested no more than 1.0 Gm. of theophylline, 0.2 Gm. of ephedrine, and 0.065 Gm. of phenobarbital. Within one hour the child was noted to be restless and hyperactive. In spite of cathartics, lavage, and general supportive therapy, the patient subsequently developed convulsions, cyanosis, and severe hematemesis. She died thirteen hours later in severe shock. Death was attributed to the toxic effects of theophylline potentiated by ephedrine.

Three years later, Pioppi,[2] unaware of Gardner's report, described the death of a 2-year-old child with asthma and bronchitis, following the rectal administration of aminophylline. The author felt that aminophylline had contributed to the patient's death in spite of an autopsy report showing "a fulminating virus infection of the lungs." Pioppi also described one case of sublethal toxicity in a 3½-year-old asthmatic boy who received one aminophylline suppository (Aminet). Frazier[3] was stimulated by Pioppi's reports to describe a third fatal case. A baby of unstated age was given aminophylline rectal suppositories at intervals of several hours. The author emphasized that hematemesis might result from aminophylline intoxication, and attributed the patient's death to this cause.

Two recent articles describe sublethal aminophylline toxicity in children. Rounds[4] in 1954 reported his experience with six cases of aminophylline toxicity in children. Two of his patients received the drug intravenously, one of these with a fatal outcome, the other developed severe toxicity but survived. Four others developed severe sublethal toxicity following enterally administered aminophylline. In 1955 Love and Corrado[5] reported five instances of nonfatal aminophylline toxicity in four children. In these authors' experience the toxic dose was usually in excess of the recommended therapeutic dose.

The present report describes four additional patients, showing varying degrees of intoxication associated with oral or rectal aminophylline therapy, and summarizes the published cases of aminophylline intoxication in childhood.

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CASE REPORTS

CASE 1.—A 23-month-old Negro male was admitted to the hospital twenty-four hours following the accidental ingestion of an unknown number of aminophylline tablets (300 mg. tablets). Twelve hours prior to admission the patient developed repeated projectile vomiting. He was awake most of the night with intermittent vomiting of clear gastric contents. In between episodes of vomiting he was described as being weak and extremely restless. The patient was hospitalized when physical examination revealed an apprehensive and hyperactive child. The vital signs were: temperature 99.2° F. (rectal), pulse 120, respirations 48, and shallow, and blood pressure 114/80. The reflexes were somewhat hyperactive, but equal bilaterally. The rest of the physical examination was within normal limits. Laboratory studies revealed hemoglobin 7.5 grams per cent, red blood cells 2.92 million, white blood cells 31,700 with 93 per cent segmentals, 6 per cent lymphocytes, and 1 per cent monocytes. $CO_2$ content was 12.5 meq. per liter, Cl 90 meq. per liter, BUN 16 mg. per cent. Urinalysis revealed a specific gravity of 1.020, 3 plus acetone, and 2 grams per liter of chloride (Fantus test). Chest roentgenograms were negative.

In the hospital the patient continued to vomit all oral fluids for the first five to six hours. He was given 15 mg. of phenobarbital and 4 c.c. of aluminum hydroxide gel every six hours. The hyperactivity present on admission gradually disappeared over a twelve-hour period, and by the end of the first hospital day he was able to tolerate a soft diet. His subsequent course was uneventful.

CASE 2.—An 18-month-old white male with asthmatic bronchitis and otitis media was seen by a private physician seven and one-half hours prior to admission to the hospital. The patient had been given parenteral penicillin in oil and started on aminophylline by rectal suppository. Shortly after the first suppository the patient became restless and extremely excited. A sedative failed to bring about evidence of improvement and the child was admitted to the hospital. Physical examination revealed an extremely active and restless child, weighing 6.8 kilograms. The pupils were widely dilated and there was minimal injection of the right tympanic membrane. The chest was clear. There were areas of atopic eczema over the legs. The patient responded to intermittent sedation and was asymptomatic within twelve hours.

CASE 3.—A 6-year-old Negro female was brought to the emergency room by her mother with the chief complaints of: (1) hallucinations and (2) the sudden onset of "spasms in her hands." The mother described the patient as talking "out of her head," in a repetitious manner, of babies and waterfalls, speaking to persons not present, and being oblivious of the presence of her family. The disturbed sensorium appeared three hours prior to hospital admission and was associated with marked physical hyperactivity, including involuntary extension of fingers and toes. Further history revealed that the child had developed an acute upper respiratory infection with bronchitis three days prior to admission. One day prior to admission she received penicillin by injection and the mother was given a prescription for aminophylline suppositories. (Later it was learned that by mistake the patient had been given a total of eight 500 mg. aminophylline rectal suppositories, or a total of 4.0 Gm. of aminophylline in a twenty-four-hour period). On this treatment the respiratory symptoms improved rapidly, but shortly after administration of the first aminophylline suppository, the patient developed anorexia, nausea, and vomiting. This vomitus was scanty, dark, unrelated to feedings, and recurred at about thirty-minute intervals until the time of admission. The patient was admitted with a tentative diag-

nosis of "toxic encephalopathy." Physical examination on admission revealed a completely uncooperative, acutely ill, wide-eyed, grimacing, hyperactive, irrational child. She babbled constantly in an incoherent manner and was continuously in physical motion to the extent that restraints were necessary for the patient's protection. The skin was warm and dry. The initial signs were: blood pressure 100/60, temperature 106° F. (R), pulse 22, respiration 28. Extraocular movements were normal (fundus examination was unsatisfactory). The nasopharyngeal mucosa was injected. There were scattered rhonchi and râles over both lung fields, with prolonged expiration. The abdomen was negative. The fingers of both hands were intermittently extended and flexed in a somewhat athetoid manner. Patellar reflexes were absent bilaterally, other deep tendon reflexes were within physiological limits, and no pathological reflexes were elicited. Response to painful stimuli was depressed.

Laboratory studies revealed: hemoglobin 14.5 grams per cent, red blood cells 6.73 million, white blood cells 20,550 with 75 per cent polymorphonuclears, 22 per cent lymphocytes, 1 per cent eosinophils, and 2 per cent monocytes. Urinalysis was negative. Cerebrospinal fluid examination revealed an initial pressure of 130 mm. of water, 2 cells per cubic millimeter, protein 37.0 mg. per cent, chlorides 120 meq. per liter.

In the hospital, phenobarbital sedation was attempted but was only partially effective. Intramuscular penicillin and intravenously administered fluids were begun shortly after admission. Six and one-half hours later the patient had a few watery stools. Shortly thereafter exacerbation of her hallucinations and shouting occurred, and she experienced a generalized convulsion lasting about five minutes. This was controlled by increased barbiturate sedation. No other seizures occurred. The initially elevated temperature fell to normal in fourteen hours. Her sensorium gradually cleared over the next thirty-six to forty-eight hours. She tolerated a soft diet on the second hospital day. A second lumbar puncture done on the fourth hospital day was normal. She was discharged asymptomatic on the fifth hospital day.

CASE 4.—This was a 7-month-old white male who was admitted to the hospital after three days of illness consisting of dyspnea, audible wheezing, and low-grade fever. These progressed in the face of penicillin injections and the administration of cough mixture. Aminophylline suppositories of unknown size were begun on an every four-hour schedule, twenty-four hours prior to admission. The patient began vomiting almost immediately after the first aminophylline suppository, and twelve hours before admission the vomitus contained brown flecks.

In the hospital, examination revealed the infant to be acutely ill, mildly dehydrated, hyperactive, and restless. Vital signs were: temperature 106° F.; pulse 180; and respiration. 60. Evidences of an upper respiratory infection were present. The chest findings were compatible with an obstructive emphysema. Scattered râles and musical wheezes were present throughout, as well as a markedly prolonged expiratory phase. Neurological examination was negative. Laboratory studies of peripheral blood and urine were normal. A lumbar puncture was negative except for an initial pressure of 300 mm. of water. Bleeding and clotting times and platelet counts were normal. Chest roentgenograms revealed moderate generalized emphysema. A diagnosis of asthmatic bronchitis was made and at this point the possibility of aminophylline intoxication was not entertained. The patient was put in humidified oxygen, and penicillin injections were continued.

Aminophylline 60 mg. was administered rectally and an intravenous

infusion of aminophylline in 5 per cent glucose was begun. Watery greenish-black streaked stools which were 2 plus positive by benzidine test were noted shortly after admission. The temperature remained elevated at 103° to 104° F. in spite of cool sponging. Eighteen hours after admission the patient was "jumpy" and restless and bilateral ankle clonus was present. Intravenous sodium Luminal 15 mg. was given with little benefit. Intermittent vomitus of "coffee-ground" material continued. At this point the possibility of aminophylline intoxication in this patient was considered and the drug was discontinued. In spite of this the patient did not improve immediately and six hours later he experienced a generalized tonic-clonic convulsion with cyanosis. This seizure continued until intravenous sodium Luminal 15 mg. was given. At this time 50 c.c. of watery "coffee-ground" material was aspirated from the stomach in an effort to relieve moderate abdominal distention and to aid respiration. His general condition improved steadily, but he continued to have minimal vomiting and passed tarry stools for three days. The hemoglobin level, however, remained normal.

### CLINICAL FINDINGS AND COMMENT

Table I summarizes the cases of aminophylline intoxication from the literature plus the four cases herein reported. The ages of the patients included range from 7 months to 6 years, with a mean age of 23 months. In the nineteen cases where sex is recorded, fifteen were males and four females. Ingestion was accidental in two instances, and its administration was directed by a physician in eighteen instances. Of the twenty instances of aminophylline poisoning in eighteen patients, four were fatal, seven were classified as severe, three were moderately severe, three were moderate, and three mild. The dose in two fatal cases is unknown. Certainly many factors influenced the final effects: individual susceptibility to the drug, variation in absorption, route of administration, and the degree of incapacity caused by the original illness under treatment. The latter factor is known to be significant in infantile salicylate intoxication since it occurs almost invariably in the sick child. In the fatal cases, one child ingested the material orally, one received the drug by vein, and two by rectal suppositories. In the cases classed as severe, four patients received the drug by rectum, one intramuscularly, and two both intravenously and rectally.

The presence of an underlying disease, generally a respiratory infection, makes it difficult to appraise the over-all effects of the drug, particularly as it effects rate and character of respirations. These were described as difficult or labored in ten instances, rapid in four, slow and deep in one, deep and pauseless in one, and shallow in one. Pulse was recorded in too few cases to make any evaluation worth while. Temperatures above normal were recorded in only six cases. It is notable that of the patients with severe hyperthermia, all three were critical and showed evidence of marked dehydration.

A common feature in all cases was some sign of central nervous system irritability. The xanthines are known to be directly stimulating to the brain cells, particularly those of the cerebrum and the medullary centers.[6] Some degree of cerebral anoxia was undoubtedly present in many of the children in acute attacks of asthma. It has been shown that theophylline

TABLE I. SUMMARY OF THE CLINICAL FINDINGS IN TWENTY CASES OF AMINOPHYLLINE INTOXICATION

| REFERENCE | AGE WEIGHT | AMINOPHYLLINE (MG./KG.)* SCHEDULE ROUTE | OTHER DRUGS | CLINICAL COURSES |
|---|---|---|---|---|
| Gardner[1] | 2 yr.<br>12 kg. | 83<br>Stat<br>Oral | Ephedrine<br>Phenobarbital | One hour after accidental ingestion, patient became emotionally upset. Heart rate normal. Dilated pupils; in 8 hr. muscular twitchings, hematemesis, seizures, cyanosis, shock, and death. |
| Pioppi[2]<br>Case 1 | 3½ yr.<br>15 kg. | (17)<br>Rectal<br>Stat | Nembutal<br>Benzocaine | Within 30 min. developed pallor, limpness, and tachycardia; responded in 3 hr. to oxygen and supportive therapy. Had appeared terminal. Dx: Asthma and bronchitis. |
| Pioppi[2]<br>Case 2 | 2 yr.<br>12 kg. | (21)<br>Stat<br>Rectal | Nembutal<br>Benzocaine | Within 3 hr.: pallor, limpness, and vomiting. Wheezing cleared but patient died in spite of supportive therapy. Author felt aminophylline intoxication contributed to death. Autopsy: Fulminating pneumonitis. |
| Frazier[3] | Baby<br>? | ?<br>?<br>Rectal | None | Developed acute vomiting progressing to hematemesis and death. Suggested after autopsy that death due to aminophylline intoxication. |
| Rounds[4]<br>Case 1 | 18 mo.<br>(11 kg.) | ?<br>Stat<br>I.V. | None | Bronchiolitis one day. Treatment given and patient immediately apneic and cyanotic. On admission critical, cyanotic, restless, albuminuria. Died 8 hr. after admission. |
| Rounds[4]<br>Case 2 | 16 mo.<br>10 kg. | 25<br>q 24 h × 3<br>Rectal | None | Dyspnea 5 days. Aminophylline administration 48 hr. prior to admission—irritable with rapid respiration, vomiting. Physical revealed dehydration, restlessness, and excitement. Recovered rapidly after sedation and supportive therapy. |
| Rounds[4]<br>Case 3 | 18 mo.<br>11 kg. | ?<br>Stat and q 2h × 2<br>I.V. | 0.1 mg. epinephrine | Wheezing all day; after therapy developed vomiting, hematemesis. Severe dehydration on admission. No respiratory distress. 14 hr. later received an aminophylline suppository followed by generalized convulsion and cyanosis, responded to sedation. EEG: Slow waves consistent with cerebral edema. Recovery slow. |
| Rounds[4]<br>Case 4 | 3 yr.<br>14 kg. | 18<br>q 8 h × 4<br>Rectal | None | Wheezing 3 days. After aminophylline, vomiting became projectile and bloody. On admission: critical, restless, dehydrated, staring, no response to painful stimuli, respirations slow and deep, few rhonchi, albuminuria. Improved in 5 hr. with supportive therapy, recovered in 29 hr. |
| Rounds[4]<br>Case 5 | 3 yr.<br>14 kg. | 7<br>Stat<br>I.V.<br>Rectal | None | Asthma not relieved by Adrenalin so aminophylline given, became restless and vomited. On admission: acutely ill, dehydrated, respirations labored, expiratory wheeze, albuminuria, hyperthermia, and hematemesis, but recovered in 24 hr. EEG: Slow waves consistent with cerebral edema, negative 3 days later. |

*Values in parenthesis are data estimated from authors' summary.

TABLE I—CONT'D

| REFERENCE | AGE WEIGHT | AMINOPHYLLINE (MG./KG.)* SCHEDULE ROUTE | OTHER DRUGS | CLINICAL COURSES |
|---|---|---|---|---|
| Rounds[4] Case 6 | 11 mo. 9 kg. | (28) Stat I.M. | None | Two days bronchitis, treated with aminophylline. Immediately restless, shrill cry, muscle twitching, facial weakness. On admission: restless, nausea, cyanotic periods, facial paralysis, afebrile, albuminuria. Generalized convulsions at 12 and 16 hr. after medication. EEG: Slow waves consistent with cerebral edema. Recovery complete. |
| Love[5] Case 1 | 15 mo. 10 kg. | 50 q 4 h × 12 25-I.V. Stat | Phenobarbital None | Severe asthma, given oxygen, phenobarbital, and aminophylline. Restless immediately. Vomiting second day; third day hematemesis, apathy, marked restlessness, muscle twitchings, dehydration. Improved 3 hr. after aminophylline stopped, fully recovered 3 days later. |
| Love[5] Case 1 | 16 mo. 10 kg. | 25 q 4 h × 6 Rectal | Epinephrine 1:100 Phenobarbital | One month later: recurrence of asthma. Treatment with rectal aminophylline followed by restlessness, repeated vomiting, lethargy and muscular twitching. Improved 5 hr. after stopping aminophylline. |
| Love[5] Case 2 | 2½ yr. 13 kg. | 19 q 6 h × 4 Rectal | Phenobarbital | Asthma. Admitted with vomiting, dyspnea, and dehydration following aminophylline. Frequent vomiting and restlessness alternating with stupor. Respirations deep and pauseless. Aminophylline discontinued, fluids given, patient greatly improved in 4 hr. |
| Love[5] Case 3 | 19 mo. 11 kg. | 22 q 8 h × 2 Rectal | Phenobarbital Benzocaine | Asthma 14 hr. Alert, apprehensive, wheezing, before medication with rectal aminophylline. On admission: vomiting and melena, wakeful but not restless, albuminuria. Symptoms subsided spontaneously. |
| Love[5] Case 4 | 2 yr. 12 kg. | 2.6 Oral q 4 h × 18 21 Rectal q 4 h × ? | Epinephrine Phenobarbital Benzocaine | Wheezing for 3 days. Hydryllin and epinephrine given at home. Admission status: Asthmatic breathing, well hydrated. Rectal aminophylline given. Vomiting, restlessness, hematemesis. Subsided with hydration and sedation. |
| Love[5] Case 5 | | 2.7 | $NH_4Cl$ | Received Hydryllin for asthma. Albuminuria and vomiting appeared. Admission status: Abdominal distention and pedal edema. BP 90/60. Received aminophylline suppository and fluids. Restlessness, emesis continued 24 hr. |
| White Case 1 | 23 mo. 10.6 kg. | (90) Stat Oral | None | In 12 hr. projectile vomiting, weak, restless; apprehensive; rapid and shallow respirations, hyperactive reflexes, cleared in 36 hr. |
| White Case 2 | 18 mo. 6.8 kg. | 36 Stat Rectal | Phenobarbital | Asthmatic bronchitis, restless, excited. Not responsive to sodium Luminal I.M. Admission status: hyperactive, pupils dilated. Given more sedation and cleared within 10 hr. |

TABLE I—CONT'D

| REFERENCE | AGE WEIGHT | AMINOPHYLLINE (MG./KG.)* SCHEDULE ROUTE | OTHER DRUGS | CLINICAL COURSES |
|---|---|---|---|---|
| White Case 3 | 6 yr. 21.5 kg. | 23 q 3 h × 8 Rectal | None | Bronchitis treated with aminophylline. Admission status: acutely ill, hyperactive, grimacing, irrational, involuntary spasm of hands, vomiting, febrile; later hallucinations, generalized convulsions, diarrhea. Lumbar puncture normal. |
| White Case 4 | 7 mo. 8 kg. | ? q 4 h × 6 Rectal | Epinephrine | Dyspnea, wheezing, fever, vomiting, and hematemesis before admission. Admission status: acutely ill, dehydrated, hyperactivity, restlessness. More aminophylline given. Ankle clonus generalized tonic-clonic convulsions, hematemesis, melena, all cleared in 5 days. |

decreases cerebral blood flow, and hence causes cerebral anoxia.[7] Petechial hemorrhages in the brain and other organs found at autopsy in Gardner's case may be explained on the basis of anoxia. Thirteen instances of "restlessness" were recorded in these twenty children with aminophylline intoxication. Four were described as excited, one other as irritable, one as emotionally upset, and two as "apprehensive." One developed muscular twitchings but no convulsions, and five experienced generalized convulsions. There was one instance of fatal diaphragmatic paralysis, and one case with facial paralysis. Our Case 3 showed extreme disorientation and grossly abnormal behavior, to the extent that the admission diagnosis was toxic psychosis. Three of Round's patients had EEG tracings; all these showed "slow waves consistent with cerebral edema."

Vomiting occurred in fifteen of the twenty instances of aminophylline intoxication described. Of these, eight developed hematemesis. Massive hemorrhage occurred terminally in two of the above. Age incidence prevents any estimate of nausea without vomiting. The presence of asthma makes the incidence of vomiting difficult to evaluate in these patients, since viscid mucus is frequently present in asthmatic patients. The mechanism of production of vomiting by theophylline is not clear, although most observers feel that it is directly irritating to the gastric mucosa. However, vomiting may be seen in association with rectal or intravenous as well as oral aminophylline therapy.

Careful studies have shown that there is no associated hyperacidity following its administration. The frequent association of nausea and vomiting in adults with a sudden drop in arterial blood pressure during intravenous aminophylline therapy suggests either that a medullary stimulation is responsible for both phenomena or that nausea and vomiting may be the result of a mild state of shock. The mechanism of the hematemesis is not clear; some hemorrhage is known to occur on the basis of direct gastric irritation and anoxia. Perhaps these factors can also ex-

plain the more extensive hemorrhages in the severe cases. Differing opinions are found regarding the effect of methylated xanthines on the clotting mechanism.[1] Venous thrombosis due to hyperprothrombinemia has been attributed to aminophylline; coagulation time has been found in other cases to be increased as long as five minutes.[1] (Gardner, quoting Scherf and Schlachmane's article).

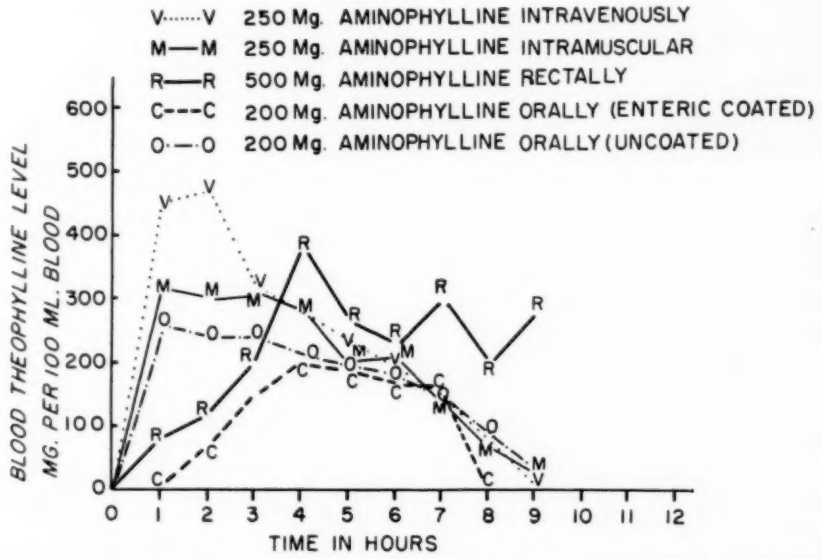


Fig. 1.—Theophylline blood levels in adult subjects following the administration of aminophylline by various routes. (Prepared from data of Waxler and Schack[8].)

Bleeding and clotting times were performed in our Case 4 and were normal. Seven patients in the reported group (Table I) showed albuminuria, but this was transient, and unassociated with other evidence of renal damage. Pedal edema was noted in one patient associated with albuminuria. This cleared spontaneously. Several patients had a urine of high specific gravity suggesting hydropenia. This may have been a factor in the development of toxicity to aminophylline.

*Toxicology.*—Except in one instance, those patients classed as "severe" or "moderately severe" and who survived received aminophylline at frequent intervals rectally or in a single large intramuscular or intravenous dose. In Gardner's fatal case, the aminophylline ingested was approximately 83 mg. per kilogram along with ephedrine 17 mg. per kilogram. Another fatal case received a single rectal dose of 21 mg. per kilogram. Neither the dosage, the number of doses, nor the route of administration can be correlated with severity.

Careful studies of the absorption and excretion of aminophylline have been carried out by Waxler and Schack.[8] They studied individually the theophylline blood levels obtained

in adults following the administration of single doses of aminophylline (Fig. 1). Oral, rectal, intravenous, and intramuscular routes were used. Although the weight of the subjects is not given by the authors, they do state that all were adults. If we assume an average subject weight of 70 kilograms then the dose used in their studies ranged from 3 to 7 mg. per kilogram of body weight. This dosage level produced a significant blood level (more than 100 $\mu$g per cent) in all subjects studied. In patients receiving the intramuscular or intravenous route of medication peak levels occurred almost immediately and persisted for seven to eight hours, while oral medication showed an absorption peak at one hour for uncoated tablets and five hours for the coated tablets with significant levels persisting for eight to ten hours. Rectal administration was variable and usually delayed one to two hours with a peak at three to five hours and significant levels still present nine hours later. For details of the range of values obtained, the reader is referred to Waxler and Schack's original publication.[8]

Study of the data in Fig. 1 reveals that no matter which route of medication was chosen, significant blood theophylline levels were still present seven to eight hours later. This implies that blood levels of theophylline are accumulative when the dosage is high or the interval of administration is frequent.

The standard pediatric texts list no oral or rectal aminophylline dosage. One suggests an intravenous dose for a 10- to 12-year-old boy of 0.25 Gm. every eight to twelve hours. This is approximately 7 mg. per kilogram of body weight. The usual adult dose is 0.5 Gm. or 7 mg. per kilogram. The frequency of dosage is not suggested in either of two medical texts consulted.

Chronic toxicity studies[9] in rabbits using 7 mg. per kilogram of body weight intravenously daily for thirty consecutive days showed no demonstrable pathology in the organs of the sacrificed animals. However, when fourteen times this dose daily (100 mg. per kilogram of body weight, or two-thirds of the $LD_{50}$ for rabbits) was given for thirty consecutive days to rabbits, and the animals then sacrificed, there was microscopic evidence of low-grade renal and meningeal irritation. (The drug was not found to be concentrated in any particular organ of sacrificed animals one hour following its intravenous administration. It was not demonstrated in the erythrocytes, and its concentration in the plasma was of the same order as that of the parenchymal organs.)

Since ephedrine is so frequently used in conjunction with aminophylline, it is felt that the potentiation of aminophylline toxicity by ephedrine should be re-emphasized. Gardner and associates[1] showed that in white rats there is a fourfold increase in the toxicity of ephedrine by the inclusion of a small dose of aminophylline, and a doubling of the toxicity of aminophylline by the administration of a relatively small dose of ephedrine. Phenobarbital decreases the excitatory effects of both ephedrine and aminophylline.

Although there are reports suggesting death from an anaphylactoid type of reaction from aminophylline,[10-12] details available on these cases are scanty. In all the cases ade-

quately described the toxic symptoms seem clearly related to an excessive dose of aminophylline.


## SUMMARY

Aminophylline (theophylline in ethylenediamine) poisoning in children was first reported in 1950. Subsequent authors have reported sixteen other instances of acute aminophylline intoxication and the present authors describe four additional cases. In this group of twenty reported cases of aminophylline intoxication there are four deaths, while ten additional children who recovered were described initially as severely ill. The widespread use of aminophylline in the management of respiratory disease in infants and children suggests that the over-all incidence of acute intoxication is not great. Nevertheless, our experience and the experience of others lead us to believe that the possibility of intoxication should be considered whenever the instituted treatment is followed by excitation, irritability, vomiting, muscle twitching, and pallor. If these early signs remain unrecognized, the patient may go on to hematemesis, convulsions, cyanosis, shock, and death.

A suggested dosage that appears to be both effective and safe is 3.5 mg. per kilogram for intramuscular or intravenous therapy, 5.0 mg. per kilogram for oral therapy, and 7.0 mg. per kilogram when given a rectal suppository. Studies of blood theophylline levels following single oral doses indicate that to prevent an accumulative effect, the frequency of dosage should not exceed every six hours and preferably be given only at seven- to eight-hour intervals. Treatment consists principally of sedation and hydration, with other supportive symptomatic therapy given as indicated by the patient's condition.


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# INCIDENCE OF RHEUMATIC FEVER IN SAN FRANCISCO CHILDREN

## A Ten-Year Study

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THE Cardiac Registry maintained by the San Francisco Department of Public Health with the cooperation and aid of the San Francisco Heart Association has made it possible to keep a record of the incidence of rheumatic fever in children in the years from 1946 through 1955.[1] In addition, this Registry has recorded the number of recurrences of rheumatic fever, the number of children hospitalized with this disease, the number of children placed in convalescent homes, and the number of children who are receiving a prophylactic drug for the prevention of recurrences of rheumatic fever in the years 1949 through 1955.

There has been an apparent decrease in the mortality rate from rheumatic fever throughout the United States and Canada in the past few years. The Metropolitan Life Insurance Company in 1943[2] reported a 70 per cent decrease in deaths due to rheumatic fever in its policyholders between the ages of 5 and 24 years in the intervals between World War I and World War II. In 1947 Keith and Pequeguat[3] reported a marked decline in the mortality rate from rheumatic fever in Canada, particularly in the age group from 5 to 20 years. In 1948 the Children's Bureau[4] reported a change in the twenty-five-year period from 1919 to 1944 with a marked decrease in the mortality rate from rheumatic fever and rheumatic heart disease among white children. This decrease was as high as 70 per cent for the age group 5 through 9 years, 64 per cent for the group 10 through 14 years, and 57 per cent for the age group 15 through 19 years. In 1951 Wolff[5] reported the comparative mortality due to rheumatic fever and heart disease in the United States between 1919 and 1921 as compared with 1944 and 1945. There was again a 70 per cent decrease in mortality from this disease in age groups from 5 to 9 years and 10 to 14 years, with a 60 per cent decrease in the 15- to 19-year age group. In 1951 Quinn and Quinn[6] reported similar data from New Haven in the years 1920 to 1948. In 1952 the Metropolitan Life Insurance Company[7] reported again that among its policyholders from 5 to 24 years of age the mortality rate from organic heart disease of all types declined from about twenty-eight to four per hundred thousand in the period from 1911 to 1950, with the mortality rate due to rheumatic fever declining from about seven to about one per hundred thousand during this period.

From the Department of Public Health, Rheumatic Fever and Congenital Heart Disease Program, and the Bureau of Maternal and Child Health. Ellis D. Sox, M.D., Director, Department of Public Health; Margaret J. Miller, M.D., Director, Bureau of Maternal and Child Health.

In 1955 Wallace and Rich[8] reported on the changing status of rheumatic fever and rheumatic heart disease in children and youth in New York City, showing that there had been a significant reduction in deaths due to rheumatic heart disease and rheumatic fever in children and youth in the past decade.

While there have been many reports regarding the decreased mortality rate from rheumatic fever and rheumatic heart disease, there have been few reports regarding the decreased incidence of this disease in the past decade. The causes for this decrease have been ascribed to (1) more accurate differential diagnosis, (2) the liberal and early use of penicillin for treatment of beta hemolytic streptococcal infections, and (3) the prevention of recurrences by the utilization of (a) a small daily dose of an antibiotic such as sulfadiazine or penicillin, or (b) the monthly injection of a long-acting penicillin. There are some who believe that the incidence of rheumatic fever may have begun its decline prior to the establishment of any of the influencing factors noted above.

The San Francisco Cardiac Registry obtains its information from the following sources:

1. The San Francisco Department of Public Health has supervision of school health in both private and parochial schools, with frequent reports to this agency by public health nurses.

2. Rheumatic fever is a reportable disease in the State of California and in San Francisco, although this is not a reliable index.

3. The San Francisco Board of Education has a rule that any child regularly attending school who is absent for any period of three days or more in any one semester must have a public health nurse visit or telephone to the home to determine the reason for such absence. The public health nurse receives a diagnosis from either the parent or the physician and refers it through channels to the Cardiac Registry.

4. Any child requiring a home teacher in San Francisco must have a request submitted by a physician with the medical diagnosis noted thereon.

5. The San Francisco Department of Public Health under the Crippled Children Services Program offers financial aid as needed to any child with rheumatic fever or rheumatic heart disease for diagnosis, hospitalization, convalescent care and treatment, including drug therapy and drugs for the prevention of recurrences. Many physicians avail themselves of the facilities of this program and thus report cases of rheumatic fever while rendering a medical report or requesting aid for his patient.

6. The San Francisco Heart Association cooperates by referring to this Registry any cases which may come to its attention through its varied educational and public relation channels.

As a result of these many sources of information the Registry has been able to obtain a report of the incidence of rheumatic fever in San Francisco, particularly in children of school age. All children who have been reported to the Registry as having had a history of rheumatic fever or rheumatic heart disease are on a time file. Every thirty days the physician caring for a child with active rheumatic fever receives a card which he may check off, noting the

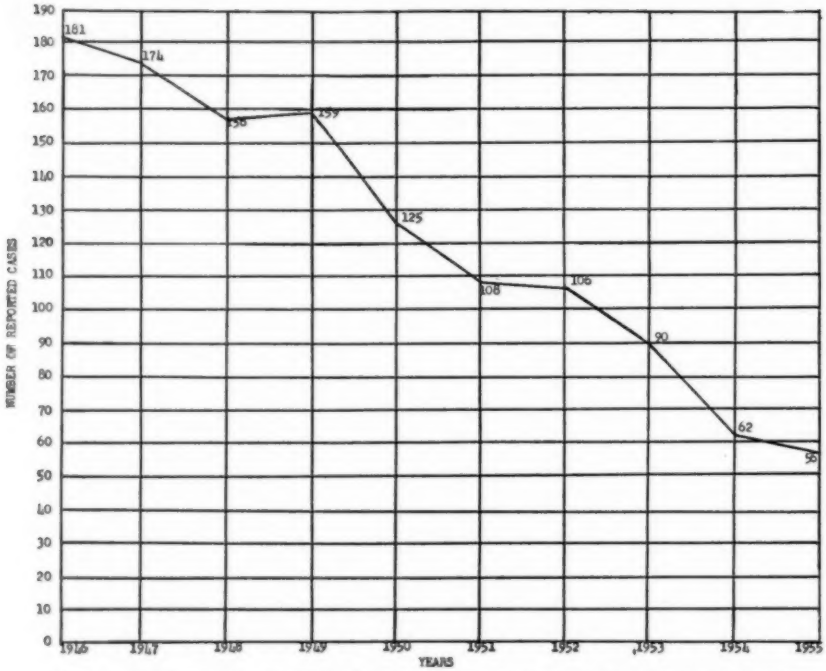


Chart I.—Total number of active rheumatic fever cases reported, 1946 through 1955.

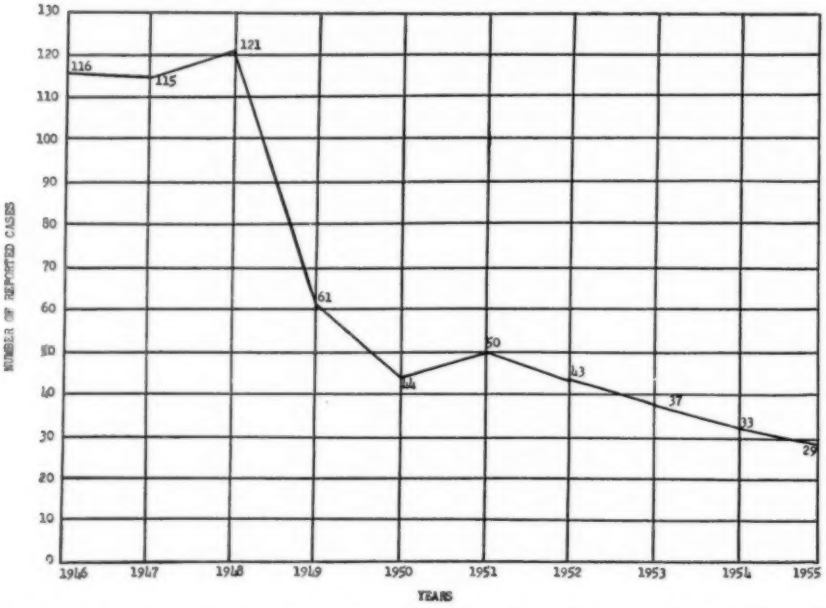


Chart II.—Number of reported cases of rheumatic fever with initial onsets during 1946 to 1955.

current status of the child. If the child has apparently recovered from rheumatic fever he is either listed as potential or history of rheumatic fever, or as inactive valvular rheumatic heart disease. The physician receives cards at six-month intervals, on which he notes the current status of such a child. If the physician reports that the child has not appeared for an examination in any significant interval of time, the social workers in the Crippled Children Services Program contact the parents and attempt to stimulate a visit to the physician as necessary.

In 1953 the Crippled Children Services Program instituted a plan for supplying prophylactic drugs to those children under its program. At that time a copy of the 1953 bulletin on *The Prevention of Rheumatic Fever and Its Recurrences* as published by The American Heart Association was mailed to every physician in San Francisco. This program of education to physicians, as well as the supplying of prophylactic drugs to those requiring them, was instituted because it was noted that the incidence of rheumatic fever had shown a steady decrease, but the relative incidence of recurrences of the disease had remained high. (See Charts III and IV.)

Chart I indicates the total number of active rheumatic fever cases reported each year and includes those patients whose onset of the disease

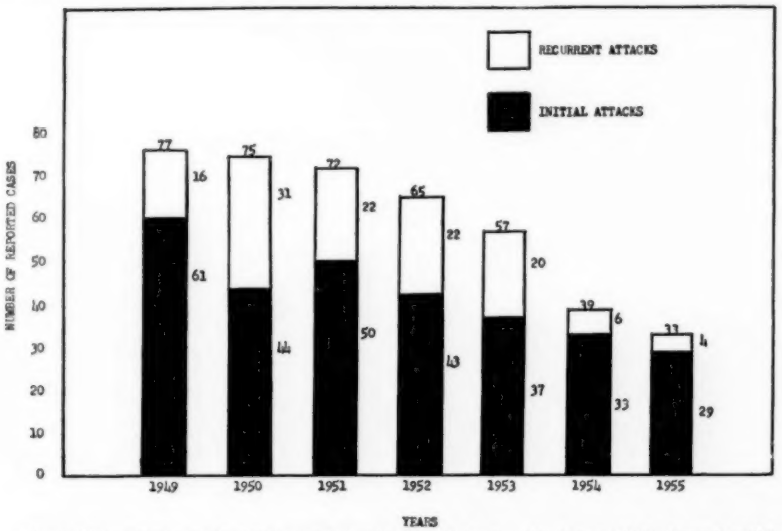


Chart III.—Total number of reported attacks of rheumatic fever, 1949 through 1955.

was during the preceding year but who still had active rheumatic fever on the first day of the succeeding year, and thus were included in the total for that year as well.

Chart II shows the number of cases of rheumatic fever with the initial onsets during that year, but does not include recurrences.

Chart III shows the relationship of recurrent to initial attacks of rheumatic fever.

Chart IV shows the number of cases of recurrent rheumatic fever reported from 1949 through 1955.

Chart V shows the number of children with rheumatic fever who were either hospitalized or placed in convalescent homes from 1949 through 1955.

with obvious valvular disease or without any apparent residual rheumatic valvular heart disease. This chart is difficult to interpret because despite the attempts to clarify the difference

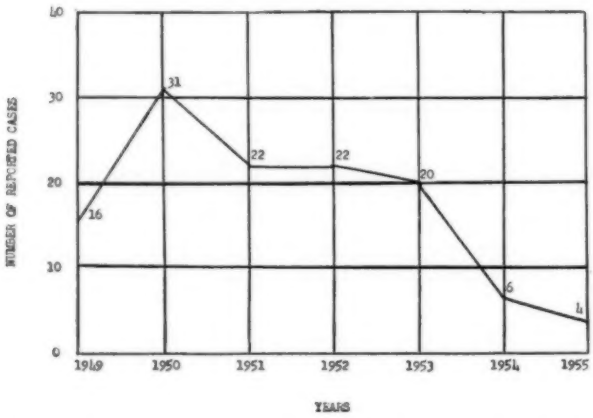


Chart IV.—Number of cases of recurrent rheumatic fever reported, 1949 through 1955.

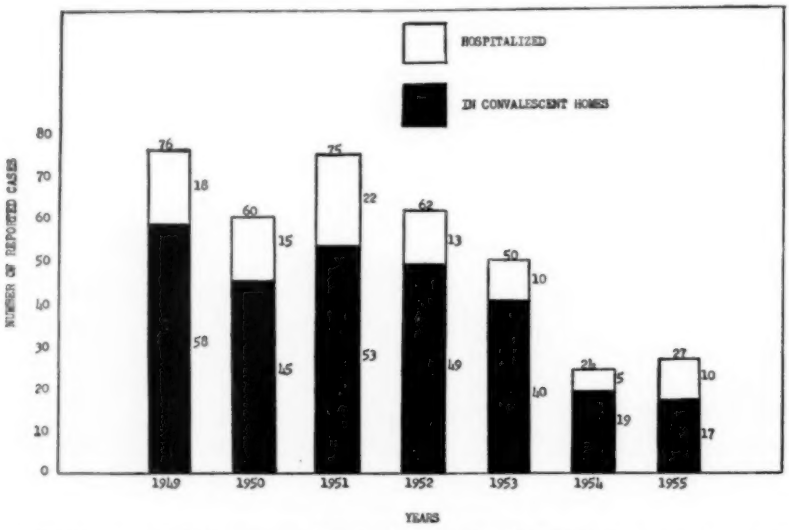


Chart V.—Number of children reported as having been hospitalized or in a convalescent home for rheumatic fever.

Chart VI shows the number of children reported as having recovered from active rheumatic fever, either

between so-called potential rheumatic heart disease and rheumatic heart disease with obvious valvular disease,

many physicians still confuse the two terms and interchange them when reporting the current status of the child.

Table I is a summation of the charts and includes as well a classification of those children who had rheumatic fever as to sex, age group, and mortality rate for those under 21 years of age.

1953, but in 1954 there was a drop from twenty recurrent cases to six recurrent cases, this decrease being maintained through 1955. In 1949 there were eighteen children hospitalized with the diagnosis of rheumatic fever, and this number declined to a low of five in 1954, although there was an increase to ten in 1955. In 1949 there were fifty-eight children

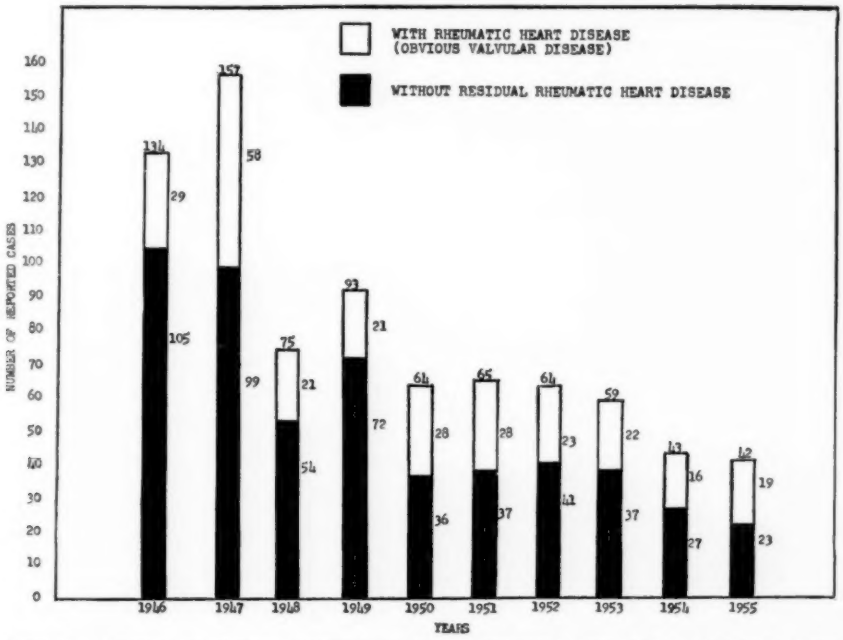


Chart VI.—Number of children reported as having recovered from active rheumatic fever, 1946 through 1955.

## DISCUSSION

From the foregoing charts and table it can be seen that there has been an appreciable reduction in the incidence of rheumatic fever in San Francisco children from 1946 through 1955. This marked decrease in the number of cases of active rheumatic fever was not paralleled by a similar decrease in the number of cases of recurrent rheumatic fever from 1949 to

in convalescent homes with the diagnosis of rheumatic fever, but in 1955 there were only seventeen such cases. The mortality rate from rheumatic fever in San Francisco has never been high. In 1949 there were five children reported as dying from rheumatic fever or its complications. In 1953 and 1954 this community had the enviable record of no deaths in children attributed to rheumatic

TABLE I. SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH—RHEUMATIC FEVER PROGRAM

Yearly Statistical Report for Ten Years (1946 Through 1955)

| | 1946 | 1947 | 1948 | 1949 | 1950 | 1951 | 1952 | 1953 | 1954 | 1955 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total number of active rheumatic fever cases during year | 181 | 174 | 156 | 159 | 125 | 108 | 106 | 90 | 62 | 56 |
| Number of children ill with rheumatic fever at beginning of year (ill during year and still ill at beginning of next year) | | | | 82 | 50 | 36 | 41 | 33 | 23 | 23 |
| Number of rheumatic fever cases with onsets during year | 116 | 115 | 121 | 61 | 44 | 50 | 43 | 37 | 33 | 29 |
| Number of recurrent rheumatic fever cases during year | | | | 16 | 31 | 22 | 22 | 20 | 6 | 4 |
| Percentage of recurrent rheumatic fever cases out of total number of reported cases during year | | | | 20.7% | 41.3% | 30.5% | 33.8% | 35.0% | 15.5% | 12.1% |
| Number of children who were hospitalized for rheumatic fever during year | | | | 18 | 15 | 22 | 13 | 10 | 5 | 10 |
| Number of children who were in a convalescent home for rheumatic fever during year | | | | 58 | 45 | 53 | 49 | 40 | 19 | 17 |
| Number of children who had rheumatic fever as to sex: | | | | | | | | | | |
| Males: | 102 | 83 | 76 | 85 | 74 | 66 | 47 | 41 | 28 | 24 |
| Females: | 79 | 91 | 80 | 74 | 51 | 42 | 59 | 49 | 34 | 32 |
| Number of children who had rheumatic fever in the following age groups: | | | | | | | | | | |
| 1- 3 | 13 | 2 | 3 | 2 | 1 | 2 | 0 | 3 | 1 | 0 |
| 4- 6 | 46 | 48 | 39 | 36 | 20 | 19 | 21 | 13 | 7 | 11 |
| 7-12 | 105 | 102 | 82 | 84 | 53 | 58 | 52 | 43 | 36 | 31 |
| 13-16 | 15 | 20 | 27 | 32 | 31 | 21 | 29 | 21 | 12 | 9 |
| 17-21 | 2 | 2 | 5 | 5 | 20 | 8 | 4 | 10 | 6 | 5 |
| Number of children who recovered from rheumatic fever | 134 | 157 | 75 | 93 | 64 | 65 | 64 | 59 | 43 | 42 |
| With rheumatic heart disease | 29 | 58 | 21 | 21 | 28 | 28 | 23 | 22 | 16 | 19 |
| Without rheumatic heart disease | 105 | 99 | 54 | 72 | 36 | 37 | 41 | 37 | 27 | 23 |
| Number of children still ill as of 1/1-- | 47 | 17 | 80 | 50 | 49 | 36 | 33 | 27 | 18 | 12 |
| Number of children who died during year | | | | 5 | 1 | 1 | 2 | 0 | 0 | 1 |

fever, but in 1955 one child with rheumatic carditis died.

## SUMMARY

Through the utilization of an active Rheumatic Fever Registry which maintains a current report of all cases of active rheumatic fever reported in the City and County of San Francisco in children up to the age of 21 years, it has been noted that there has been an appreciable decrease in the number of active rheumatic fever cases from 1946 through 1955, an interval of ten years. This has been accompanied by a decrease in the number of children who were hospitalized or were placed in convalescent homes with this condition during these years, and particularly from 1949 on. At the same time it was noted that the number of cases of recurrent rheumatic fever remained relatively high until 1954 when, after an educational campaign for physicians and lay persons and with the availability of prophylactic drugs through the Crippled Children Services Program, there was an appreciable drop which maintained itself through 1955.

## CONCLUSION

An analysis of the statistics maintained by a Rheumatic Fever Registry instituted by the San Francisco Heart Association and maintained by the San Francisco Department of Public Health indicates that there has been a decrease in the incidence of rheumatic fever in San Francisco school children. There has been a much slower decrease in the number of cases of recurrent rheumatic fever, but apparently since the advent of a campaign of education of physicians and parents regarding the use of penicillin or sulfa drugs for the prevention of these recurrences, as well as the increased availability of these drugs through a program originated by the State of California Crippled Children Services, there has been an appreciable decrease in the number of recurrences as well. Thus there has been a decrease in the incidence of a disease which at one time was considered to be the most common cause of death in children between the ages of 5 and 15 years. Rheumatic fever is apparently beginning to assume a much less important role not only in mortality but in morbidity, as evidenced by the above figures. However, the problems involved in the recognition of rheumatic fever are still great, its management has still not been stabilized, and there must be no diminution in the measures necessary to suppress this disease.

I wish to thank Miss Ruth Rieve for her help in the preparation of this paper.

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# POLIOMYELITIS IN PREGNANCY: EFFECT ON FETUS AND NEWBORN INFANT

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ACCORDING to published data on poliomyelitis during pregnancy, the fetus may be affected either directly by the viral agent or indirectly by the adverse conditions associated with maternal disease.

Infection of the fetus can presumably occur during the viremia stage of maternal infection.[1, 2] Evidence supporting this was recently reported in the case of a fetal death occurring nine days after the onset of maternal symptoms of poliomyelitis.[3] Type I virus was isolated from both the placenta and fetus. The cause of the fetal death was unknown, because secondary or unrelated factors could not be ruled out.

Most of the fetal deaths reported in the literature in pregnancies complicated by poliomyelitis have followed maternal infection in the first trimester of pregnancy. Infection in later stages of pregnancy has usually been followed by a live birth. The over-all frequency of fetal deaths has varied from 20 to 35 per cent of maternal infections.[4-14] These rates were said to be either within or above the average limits of expectancy.

With respect to other fetal changes following maternal infection, no evidence of an increased incidence of congenital defects has been cited in the literature. An increase in the frequency of prematurity has been noted following maternal infection in the first and second trimesters.[11, 14] In most instances, however, the fetus did not appear to be underdeveloped.

If the fetus survives the immediate effects of maternal infection, life in utero can be threatened by the failure of maternal respiration or circulation in cases of bulbar poliomyelitis. Fortunately, such cases are rare, and the life of the baby can usually be saved by adequate medical care.

In recent years, evidence of an additional hazard has become apparent. When poliomyelitis occurs shortly before delivery, the fetus may be infected from maternal sources, not only in utero but also during delivery by fecal contamination of the birth canal and operative field. In such cases the infant may develop signs of poliomyelitis early in the neonatal period.[15-21] Extramaternal sources of infection may also be implicated after birth as noted in a report of an outbreak of poliomyelitis among newborn infants.[22]

The foregoing aspects of the problem and others were considered in the present investigation of the effects of maternal infection on the developing fetus. The data were ob-

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tained in the course of a prospective study of poliomyelitis and pregnancy in New York City from 1949 to 1953, inclusive.[23] During this five-year period, eighty-seven cases of poliomyelitis were observed in pregnant women, of which twenty-three were nonparalytic and sixty-four paralytic types of the disease. The patients were seen by diagnosticians within a week after notification of the disease for the collection of clinical and epidemiological data. Subsequently, they were revisited one to two months after onset to check on the pregnancy status, and a year after delivery for information on the newborn infant. Data on the condition of the newborn infant at time of birth were obtained from copies of the confidential birth certificate.

TABLE I

| OUTCOME OF DELIVERY | OBSERVED RESULTS | | EXPECTED RESULTS | |
|---|---|---|---|---|
| | NUMBER | PER CENT | NUMBER | PER CENT |
| Fetal deaths* | 19 | 21.6 | 8.6 | 9.7 |
| Live births | 69 | 78.4 | 79.4 | 90.3 |
| Congenital defects | 1 | 1.1 | 0.7 | 0.8 |
| Premature infants | 11 | 12.5 | 6.4 | 7.3 |
| Normal | 57 | 64.8 | 72.3 | 82.2 |
| Total | 88 | 100.0 | 88.0 | 100.0 |

*Refers to all fetal deaths regardless of duration of gestation.

## RESULTS

1. *General Considerations.*—A total of eighty-eight products of conception were studied in the eighty-seven pregnancies complicated by poliomyelitis. There were eighty-six single births and one set of twins. The outcome of these pregnancies as compared with the expected outcome based on data reported in the general pregnant population during the period under consideration is shown in Table I. The observed number of fetal deaths was more than twice that expected based on natality statistics for New York City from 1949 to 1953, inclusive.[24] However, adjustment for underreporting of fetal deaths increases the expected number to about 12.5 or more, and reduces the difference between observed and expected results below the level of statistical significance.* [25] There was no evidence of an increase in cases of congenital defect—only one case was reported for a frequency of 1.1 per cent. The number of premature infants appeared to be increased. However, the difference between the observed and expected number was too small to be considered statistically significant. The apparent increase in fetal deaths and in premature infants was not related to racial factors, because only six of the eighty-eight births were Negroes. Of these six births, one was premature, three were normal, and two were fetal deaths. Thus, they represented 7 per cent of the total sample and 10 per cent of the fetal deaths and premature infants, respectively.

An analysis of the foregoing data by clinical type of maternal disease during gestation is given in Table II. There were relatively fewer fetal deaths and more premature infants following an attack of paralytic poliomyelitis during pregnancy than nonparalytic poliomyelitis. However,

*A probability of less than 0.05 was considered significant in the present study.

the respective differences were not considered statistically significant for the number of cases in each group, particularly the few cases in the nonparalytic group.

The effects of other factors on the results observed at birth were considered, such as parity and the degree of epidemicity or incidence of poliomyelitis in the general population when maternal infection occurred. A summary of the analysis of the data by these factors is given in Table III. The percentage of fetal deaths and premature infants was slightly greater in the epidemic year of 1949 than in the succeeding nonepidemic years. These percentages also appeared to be greater among primiparous women than multiparous women. However, the differences were not statistically significant for the small samples considered. Thus, the groups studied were too small to exclude the likelihood of sampling variation, and larger samples would be needed to evaluate adequately the effect of the foregoing factors.

2. *Poliomyelitis in the Newborn Infant.*—Three cases of paralytic poliomyelitis were reported in the neonatal period among the sixty-nine live births in the study, a rate of 43 per 1,000 live births. The three cases occurred among the fifty-four newborn infants of mothers with paralytic poliomyelitis, a rate of 56 per 1,000 live births in this group. The attack rate of paralytic poliomyelitis exceeded that recorded for

TABLE II

| OUTCOME OF DELIVERY | CLINICAL TYPE OF MATERNAL DISEASE | | | |
|---|---|---|---|---|
| | PARALYTIC | | NONPARALYTIC | |
| | NUMBER | PER CENT | NUMBER | PER CENT |
| Fetal deaths | 11 | 16.9 | 8 | 34.8 |
| Live births | 54 | 83.1 | 15 | 65.2 |
| Congenital defects | 1 | 1.5 | 0 | 0.0 |
| Premature infants | 10 | 15.4 | 1 | 4.3 |
| Normal | 43 | 66.2 | 14 | 60.9 |
| Total | 65 | 100.0 | 23 | 100.0 |

TABLE III. OUTCOME OF PREGNANCY FOLLOWING POLIOMYELITIS DURING GESTATION IN RELATION TO DEGREE OF EPIDEMICITY AND PARITY AT TIME OF ONSET

| FACTOR CONSIDERED | OUTCOME OF PREGNANCY | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TOTAL | | FETAL DEATHS | | LIVE BIRTHS | | | | | |
| | | | | | CONGENITAL DEFECTS | | PREMATURE | | NORMAL | |
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| *Epidemicity at Time of Onset of Maternal Poliomyelitis* | | | | | | | | | | |
| Onset in epidemic year (1949) | 28 | 100.0 | 7 | 25.0 | 0 | 0.0 | 4 | 14.3 | 17 | 60.7 |
| Onset in nonepidemic years (1950-1953) | 60 | 100.0 | 12 | 20.0 | 1 | 1.6 | 7 | 11.7 | 40 | 66.7 |
| Total | 88 | 100.0 | 19 | 21.6 | 1 | 1.1 | 11 | 12.5 | 57 | 64.8 |
| *Parity at Time of Infection* | | | | | | | | | | |
| Primiparas | 19 | 100.0 | 5 | 26.3 | 0 | 0.0 | 3 | 15.8 | 11 | 57.9 |
| Multiparas | 69 | 100.0 | 14 | 20.3 | 1 | 1.4 | 8 | 11.6 | 46 | 66.7 |
| Total | 88 | 100.0 | 19 | 21.6 | 1 | 1.1 | 11 | 12.5 | 57 | 64.8 |

any age group of familial contacts in New York City during the period considered, and is more than 1,000 times greater than the rate of paralytic poliomyelitis observed under 1 year of age in the general population.[26, 27]

The three cases observed in the study occurred among nine newborn infants following maternal infection in the last month of gestation. All three infants were delivered within twenty-four to forty-eight hours of the onset of neurological signs of poliomyelitis in the mother. Symptoms of paralysis in the newborn infant were observed from six to ten days after delivery. Two died at age 11 and 13 days, respectively, and one recovered with mild paralysis of the right arm.

3. *Neonatal Mortality.*—There were five deaths in the neonatal period among the sixty-nine live births, a death rate of 72.5 per 1,000 live births as compared with an expected neonatal death rate of 18.6 per 1,000 live births.[24] All of the deaths were associated with the paralytic type of poliomyelitis in the mother during gestation. When based on these cases only, the neonatal death rate was 92.6 per 1,000 live births.

One of the deaths occurred in the single case of congenital defect reported in the study, that of a monstrosity weighing 2,150 grams at birth who lived a few minutes only. The mother was 27 years of age, had had one normal delivery and no fetal deaths previously. She developed paralytic poliomyelitis during the sixth month of gestation and delivered at term three months after infection.

All the other deaths in the neonatal period were related directly or indirectly to poliomyelitis in the mother. Two died within twenty-four hours of "anoxemia," following post-mortem cesarean delivery in mothers dying of bulbar poliomyelitis in the eighth and ninth months of gestation, respectively. Two other deaths occurred in newborn infants with neonatal poliomyelitis who developed paralysis ten days after birth and died at ages 11 and 13 days, respectively, as already noted. In these two cases, the mothers developed characteristic symptoms of poliomyelitis on the day of delivery or within twenty-four hours after delivery.

No deaths occurred in the post-neonatal period. The total number of newborn infants alive at 1 year of age was sixty-four or 72.7 per cent of all the products of gestation in the study. None showed any gross evidence of congenital deformity, and all were well developed at the end of their first year. No clinical evidence of poliomyelitis was reported in the post-neonatal period.

From the results described above, there was evidence of an increased incidence of neonatal poliomyelitis and mortality which was associated with the onset of maternal infection in the last months of pregnancy. No conclusions could be drawn as to the over-all incidence of fetal deaths and premature births following poliomyelitis in pregnancy since the data were inconclusive. The results observed were studied more closely for a possible relationship to the period of gestation at onset of infection.

4. *Period of Gestation at Onset of Poliomyelitis.*—An analysis of the

data according to length of gestation revealed that the time of onset of clinical infection was a major influence in the outcome of pregnancy. This is apparent from the distribution of the products of gestation shown in Table IV by the trimester of infection, for all clinical cases of poliomyelitis in the mother, and for paralytic cases only. As noted in Table IV, the frequency of fetal deaths decreased markedly with trimester of onset of poliomyelitis from 46.7 per cent of all clinical infections in the first trimester to 11.4 per cent of those in the second trimester and to 4.3 per cent in the third. Based on paralytic cases only, the fetal death rates by trimester of infection were 35, 12, and 5 per cent, respectively. On the other hand, the percentage of normal infants at birth increased progressively with trimester of onset of paralytic maternal infection from 50 per cent in the first trimester to 85 per cent in the last. The frequency of premature infants fluctuated between 10 and 20 per cent per trimester of onset of poliomyelitis with the highest rate after maternal infection in the second trimester.

The results obtained by trimester of infection were further examined to determine the time relationship between the onset of maternal disease and the delivery of the product of

TABLE IV. OUTCOME OF PREGNANCY BY TRIMESTER OF GESTATION AT TIME OF ONSET OF POLIOMYELITIS

| OUTCOME OF PREGNANCY | PERIOD OF GESTATION AT ONSET OF POLIOMYELITIS | | | | | |
|---|---|---|---|---|---|---|
| | FIRST TRIMESTER | | SECOND TRIMESTER | | THIRD TRIMESTER | |
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| *All Clinical Cases* | | | | | | |
| Fetal deaths | 14 | 46.7 | 4 | 11.4 | 1 | 4.3 |
| Live births | 16 | 53.3 | 31 | 88.6 | 22 | 95.7 |
| Congenital defects | 0 | 0.0 | 1 | 2.9 | 0 | 0.0 |
| Premature infants | 3 | 10.0 | 6 | 17.1 | 2 | 8.7 |
| Normal | 13 | 43.3 | 24 | 68.6 | 20 | 87.0 |
| Total | 30 | 100.0 | 35 | 100.0 | 23 | 100.0 |
| *Paralytic Cases Only* | | | | | | |
| Fetal deaths | 7 | 35.0 | 3 | 12.0 | 1 | 5.0 |
| Live births | 13 | 65.0 | 22 | 88.0 | 19 | 95.0 |
| Congenital defects | 0 | 0.0 | 1 | 4.0 | 0 | 0.0 |
| Premature infants | 3 | 15.0 | 5 | 20.0 | 2 | 10.0 |
| Normal | 10 | 50.0 | 16 | 64.0 | 17 | 85.0 |
| Total | 20 | 100.0 | 25 | 100.0 | 20 | 100.0 |

TABLE V

| PERIOD OF GESTATION AT ONSET OF POLIOMYELITIS | NUMBER OF FETAL DEATHS | INTERVAL BETWEEN ONSET OF POLIOMYELITIS AND ONSET OF LABOR | | |
|---|---|---|---|---|
| | | LESS THAN 2 WK. | 2 TO 4 WK. | 1 OR MORE MO. |
| First trimester | 14 | 9 | 1 | 4 |
| Second trimester | 4 | 1 | 0 | 3 |
| Third trimester | 1 | 0 | 1 | 0 |
| Total | 19 | 10 | 2 | 7 |

conception. A summary of the interval elapsing between the onset of poliomyelitis and labor where fetal deaths occurred is given in Table V. In ten of the nineteen cases where fetal deaths resulted, labor occurred within two weeks after the onset of poliomyelitis in the first and second trimesters. These deaths may have been related to the occurrence of poliomyelitis in the mother. No other specific causes were mentioned in the records examined. In addition, two fetal deaths occurred from two to four weeks after onset of maternal infection in the first and third trimesters, respectively. The former was not associated with any other complication of pregnancy and may have been related to the infection. The latter, however, occurred in a mother who died of eclampsia in the last month of gestation and cannot be directly attributed to poliomyelitis. In seven other cases the interval between the onset of polio and delivery was one or more months. In these cases, the onset of labor appeared to be too far removed from the onset of poliomyelitis for the infection to be a direct precipitating factor and other complications of pregnancy should be considered.

In summary, therefore, the time relation between the occurrence of poliomyelitis and fetal death was sufficiently close in eleven of the nineteen deaths to suggest a direct relationship between infection and the ensuing fetal death. Ten of these eleven deaths were associated with infection in the first trimester. The eleven deaths included four out of eight fetal deaths following nonparalytic poliomyelitis and seven out of eleven fetal deaths after paralytic disease.

With respect to the premature infants, the interval between infection and the onset of labor in the mother was usually more than a month as summarized in Table VI. In the case of nine of the eleven premature infants, maternal infection occurred in the first and second trimesters, and delivery followed more than a month after infection. Six of these nine infants were delivered between the thirty-eighth and fortieth weeks of gestation, and one each at twenty-nine, thirty-four, and thirty-six weeks of gestation. Two premature infants were born within a week after the onset of poliomyelitis in the mother. In both cases, infection occurred in the thirty-ninth week of gestation. In only two instances, therefore, did the onset of labor follow shortly after infection, but these occurred in pregnant women infected at term. In all other cases of premature infants gestation did not appear to be interrupted by infection and usually continued to term. All but one of the

TABLE VI

| PERIOD OF GESTATION AT ONSET OF POLIOMYELITIS | NUMBER OF PREMATURE INFANTS | INTERVAL BETWEEN ONSET OF LABOR AND ONSET OF POLIOMYELITIS | | |
|---|---|---|---|---|
| | | LESS THAN 2 WK. | 2 TO 4 WK. | 1 OR MORE MO. |
| First trimester | 3 | 0 | 0 | 3 |
| Second trimester | 6 | 0 | 0 | 6 |
| Third trimester | 2 | 2 | 0 | 0 |
| Total | 11 | 2 | 0 | 9 |

mothers of the premature infants had the paralytic type of poliomyelitis.

In addition to the two premature infants mentioned, nine normal infants were born shortly after the occurrence of poliomyelitis in the last trimester of pregnancy. In most instances, symptoms of poliomyelitis occurred in the ninth month of gestation or near term, and labor began spontaneously less than a week after the onset of disease. The significance of the onset of labor early in the acute stage of maternal disease is that the newborn infant is exposed to a high risk of clinical infection, as noted in the section on neonatal poliomyelitis.

## DISCUSSION

The present study represents a prospective investigation of the effects of poliomyelitis during gestation on the fetus and newborn infant. Because of the rarity of poliomyelitis in females of childbearing age, it was necessary to plan the study over a period of years, beginning with the epidemic of 1949 in New York City and continuing through the succeeding four nonepidemic years. During this period, the annual attack rate of poliomyelitis in women from 15 to 44 years of age varied from 4.9 to 13.5 per 100,000 in endemic and epidemic years, respectively. These variations allowed for a comparison of the effects of different rates in the same community.

There appeared to be no statistically significant difference in the outcome of delivery as measured by the frequency of fetal deaths, premature infants, and normal live births between years of high and low incidence. Nor was the outcome significantly affected by the clinical type of disease in the pregnant woman except for the occurrence of bulbar poliomyelitis. However, the number of cases studied was too small for adequate evaluation of these factors. Similarly, inconclusive results were obtained in the analysis of the cases observed by such contributory factors as race, parity, and previous fetal deaths.

There was no evidence of an association between poliomyelitis in pregnancy and the occurrence of congenital defects. Only one such case was reported in eighty-eight deliveries in the study, that of a monstrosity associated with paralytic poliomyelitis in the mother in the sixth month of gestation, and born at term weighing 2,150 grams. The data reported included eight maternal cases of poliomyelitis with onset of disease in the first two months of pregnancy, when the expected incidence of congenital defect is highest, twenty-two cases infected in the third month of gestation, and fourteen in the fourth month, a total of forty-four cases in the first four months of gestation, thirty-one with paralytic disease, and thirteen with nonparalytic disease.[23]

It was possible to establish a definite relationship between some of the results observed in the fetus and newborn infant and the period of pregnancy in which infection occurred. Infection in the first trimester was associated with fetal deaths in almost half of the cases infected at this time and with immature live births in an additional 10 per cent. The frequency of fetal deaths dropped sharply from 46.7 per cent following infection in the first three months of pregnancy to 13.8 per cent for infec-

tions in the fourth and fifth months and to 3.4 per cent after that. Not only was there a preponderance of fetal deaths following infection in the first trimester but about 65 per cent of these occurred within two weeks of the infection and were apparently directly related to the occurrence of poliomyelitis in the mother. For infections occurring after the first trimester, the interval between the onset of infection and the onset of labor was usually one or more months, thus implicating other factors in pregnancy as the possible causes of the fetal deaths.

Most of the premature infants observed in the study were associated with infection in the first and second trimesters. In most of these cases, gestation proceeded to term, labor usually occurred more than a month after the onset of infection, and other complications of pregnancy were not reported. In view of the many causes of prematurity, one can only speculate on the possibility that the effect of infection on the fetus was not marked enough to kill it, but did influence its growth.

The onset of poliomyelitis in the last trimester was associated with a live birth in 96 per cent of the pregnancies. There was only one fetal death in twenty-three cases in this group. This occurred sixteen days after the onset of poliomyelitis in the last month of gestation, in a woman who died of eclampsia.

Two additional observations of clinical and epidemiological interest were noted among those infected in the last stages of pregnancy. First, neonatal poliomyelitis occurred only in infants whose mothers developed poliomyelitis near term, and who were born shortly after onset of the disease in their mothers. This group is presumably unprotected by maternal antibodies, and may be heavily exposed to maternal infection in utero, during delivery and after birth.

Second, two newborn infants delivered by post-mortem cesarean section died of "anoxemia" in less than fourteen hours. The mothers had died of bulbar poliomyelitis in the eighth and ninth months of gestation, respectively. The occurrence of bulbar poliomyelitis is a serious complication which threatens the life of both the mother and child. Death of the child may be avoidable by timely cesarean section.[14]

There were four deaths in the neonatal period which were attributable to the onset of poliomyelitis in the mother toward the end of pregnancy. In two, the mothers died before delivery and a post-mortem cesarean section was done in a vain effort to save the child. In two others, the infant developed poliomyelitis shortly after birth.

## SUMMARY

1. A prospective study was made of the outcome of gestation following the occurrence of poliomyelitis in New York City from 1949 to 1953, inclusive. During this period eighty-seven pregnancies, which resulted in eighty-eight products of gestation, were investigated. Sixty-five fetuses were associated with paralytic poliomyelitis during gestation and twenty-three with nonparalytic poliomyelitis.

2. There was no evidence of an increase in congenital defects, and inconclusive evidence of an increase in prematurity.

3. Fetal deaths were observed in from 35 to 46 per cent of the preg-

nancies complicated by the onset of poliomyelitis in the first trimester of gestation. Most of these fetal deaths were delivered within two weeks of the onset of clinical infection, and appeared to be directly related to the occurrence of poliomyelitis in the mother.

4. An increase in the incidence of neonatal poliomyelitis was observed which was associated with paralytic maternal infection shortly before delivery.

5. An increase in the neonatal mortality rate was noted which was related to neonatal poliomyelitis and to anoxemia following post-mortem cesarean section in women dying of bulbar poliomyelitis.

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# MEGACOLON AS A MANIFESTATION OF FAMILIAL AUTONOMIC DYSFUNCTION

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IN 1949 a group of remarkable children was described by Riley and associates,[9] which consisted of a diffuse autonomic dysfunction usually occurring in Jewish children with a frequent familial incidence. The term "familial autonomic dysfunction" has been used to designate the syndrome which is probably a congenital neurological disorder involving the autonomic and somatic nervous systems and the general growth pattern.

Since 1949, nearly fifty cases have been reported, most of them forming an extension by Riley and co-workers of the original group of five. Genetic aspects of the disorder were emphasized by St. Martin.[12] Later studies by Riley and his group[11] have concentrated on the psychological and social factors surrounding the syndrome. More recently Moloshok and Reuben[7] reported thirteen cases typical of the syndrome and Linde[6] reported a typical case occurring in a non-Jewish child.

The present report adds one more case to those previously described. It is typical in all features except that the patient entered the hospital because of megacolon and, in addition, is not of Jewish background.

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## CASE REPORT

R. G., a 3-year-old white boy, was referred to the University of Illinois Research and Educational Hospital because of a scoliosis of one-year duration and "bowel trouble" since 3 months of age.

The patient was born prematurely after a twenty-eight-week gestation, with a birth weight of 1,425 grams. During the neonatal period there was no clinical evidence of congenital anomalies or symptoms referable to the respiratory, gastrointestinal, or central nervous systems.

At 3 months of age he developed a pneumonia requiring hospitalization and blood transfusions. After a difficult course he recovered, but it was noticed shortly after discharge from the hospital that his abdomen was distended. The mother stated that the patient's bowel movements occurred two to three times per week and consisted of a large amount of hard feces. Between these large bowel movements there was fecal incontinence with fecal staining of diapers. This pattern of bowel habits continued up to the time of admission to the hospital.

Approximately one year before admission the mother noted the gradual onset of curvature of the spine which became apparent after the child began to stand. The parents felt that the spinal curvature had become progressively worse in the past six months.

The patient's development was generally slow. He talked first at 2½ years of age and did so only poorly on entry at age 3. Crawling began at 2, and walking at 3 years of age. He was not toilet trained and soiled many diapers daily. Few toilet-training attempts had been made by the parents.

The patient's mother was of French descent which could be traced back at least four generations. The father's parents were Scots. Their ancestors had lived in Kentucky and Indiana for several generations. There was no history of Jewish ancestry on either side. The mother's side was free of related diseases. However, there was a strong history of a form of familial paraplegia in the father's family. This was called "Tetter's disease" by the family. The father's mother (patient's paternal grandmother) became paraplegic sometime in her middle years and died several years later after quadriplegia had developed. This grandmother had four siblings. Two of these, males, died in infancy. The surviving brother and sister lived to maturity. Both of them eventually developed a similar paraplegia, were bedridden, and died quadriplegic.

The patient was the youngest of six children. All of the siblings were said to be entirely normal except for one. This child, a brother, 8 years of age, was described by the mother as possibly similar to the patient. He was slow in school, irritable, with poor speech, drooled, and had blotchy skin. However, when we examined him we found no drooling, normal weight and height, no indifference to pain, normal reflexes, clear speech, and clear skin.

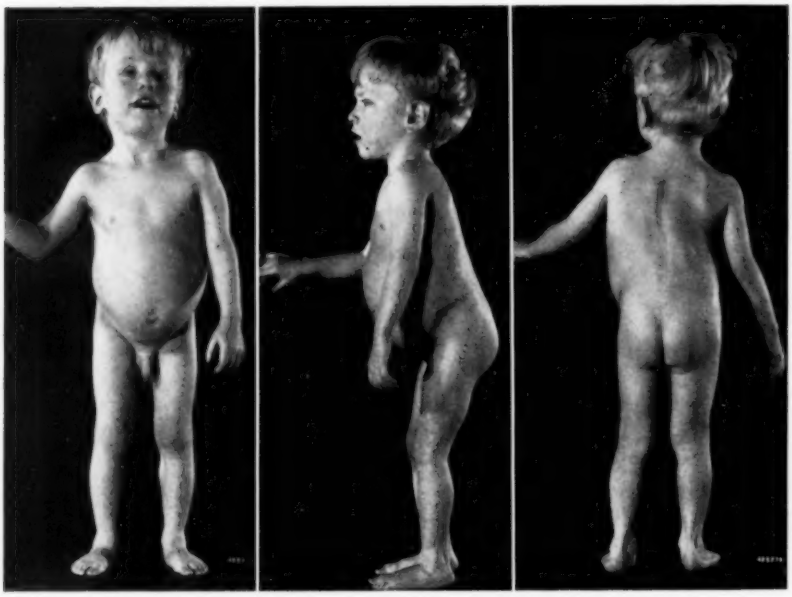

Fig. 1.—Frontal, lateral, and dorsal views of patient, showing particularly drooling, enlarged abdomen, pattern of marmorization of lower extremities, and dorsal scoliosis.

Patient's siblings were all older, and as the youngest and the invalid of the family he received a good deal of attention. Parents felt that he had been overindulged and gratified by virtue of his sickness and temper

tantrums to an unhealthy extent. An older sister devoted much of her time to his care and entertainment. The parents were easy-going, mild-mannered, and limited financially.

*Physical Examination.*—The patient was a thin, underdeveloped white male (Fig. 1) who appeared to be very irritable and who drooled heavily.

Blood pressure was 120/65, pulse 100, respiration 20. The length was 83 centimeters, weight 11.8 kilograms, head 48 centimeters, chest 51 centimeters.

Although the patient was 3 years of age, the height and weight were in the 3rd to 10th percentile for a 2-year-old child. The head was asymmetrical with protruding left parietal boss. Eyes were normal, fundi normal. Corneal reflexes were not present. Lacrimation was adequate to keep conjunctiva moist; however, during numerous emotional upsets tearing was sufficiently diminished that only three tears were actually seen. There was a chronic nasal discharge. The lungs were clear. The heart was normal. The abdomen appeared distended and filled with several hard masses formed by feces-filled sigmoid, descending, and transverse colon. Rectal examination revealed the sphincter to be relaxed and the ampulla filled with hard feces. On neurological examination the cranial nerves were intact with the exception of loss of corneal reflexes. The deep tendon reflexes were hypoactive. There was a marked lack of response to pinprick. The gait was broad based and unsteady, immature rather than cerebellar in type.

Examination of the musculoskeletal system revealed right dorsolumbar scoliosis, a rounded back, and bilaterial pes cavus. Muscles were generally hypotonic, joints loose and readily hyperextensible.

The skin was blotchy, especially over the extremities. This exaggerated marmorization was particularly evident during emotional outbursts.

*Laboratory Data.*—Since the patient entered the hospital because of "bowel trouble," our initial studies focused upon the gastrointestinal tract. Barium enema (see Fig. 2) revealed marked dilatation of the colon with no areas of constriction present. This was confirmed under fluoroscopy, using the Newhauser technique.[13] Barium meal studies and intravenous pyelogram done concomitantly were normal. Stools contained trypsin and were negative for ova and parasites.

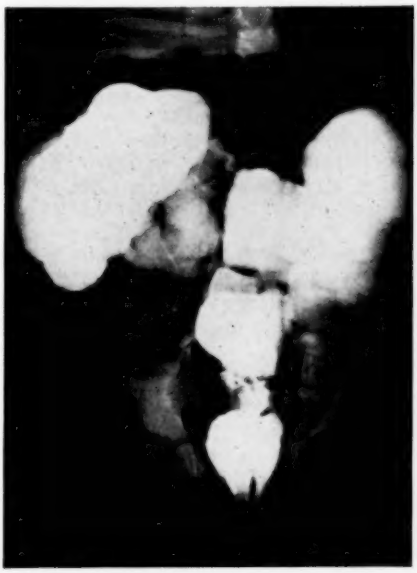

Fig. 2.—Barium enema showing marked dilatation of the colon with no areas of constriction present.

Because of the megacolon the urinary tract was investigated. There was a residual urine of 150 c.c. found on three occasions. Subsequent cystometrograms and cystoscopy were found to be normal.

Routine laboratory studies including urinalysis, white count, red count, and differential were normal. Blood chemistries (nonprotein nitrogen, Na, Cl, K, Ca, $CO_2$, protein) were normal. Nose and throat culture on admission showed beta hemolytic streptococci.

Chest x-rays showed small multiple nodular densities present in the mid and proximal lung fields. Skin tests for tuberculosis, histoplasmosis, and coccidioidomycosis were negative.

X-rays of the spine showed a mild scoliosis in the dorsal and lumbar segments.

Pain intolerance noted shortly after admission led to special neurological testing. Lumbar puncture; opening pressure 190 mm. Hg, closing pressure 170 mm. Hg. The fluid was clear, no cells were present, and the culture was negative. Colloidal gold curve was 000,000,0000. Kahn and Wassermann tests were negative. Protein was 11 mg., glucose 33 mg., chloride 123 meq. Electroencephalogram revealed 7 to 8 per second activity during drowsiness and sleep spikes from right temporal area sometimes spreading to right parietal. There were frequent sharp negative and positive left and right frontal, left temporal and sometimes parietal area, 14 per second positive spikes maximal in the right hemisphere.

*Developmental Studies.*—Evaluation of motor, verbal, and social skills left the impression that the patient functioned at about the 2-year level. He was able to manage stairs up and down, but could not jump or kick. He could combine his twenty-word vocabulary into two- and three-word sentences and name a few objects, but spoke with poor articulation. He could feed himself and handle a cup. He related well to staff and played with the other children, but only after a considerable period on the ward. When first seen these traits were obscured by frightened petulant behavior.

## DISCUSSION

Riley[10] in 1952 discussed in considerable detail the many symptoms and signs found in familial autonomic dysfunction. He divided them into two groups—common features found in 97 to 100 per cent of his cases, and those occurring less often, in 35 to 85 per cent. As summarized in Table I, our case is so clearly typical that little more need be said in defense of the diagnosis. More deserving of discussion are the two features of this case making it unlike the usual: megacolon as a presenting symptom, and the absence of Jewish background.

An extensive review of the literature has failed to turn up any previous case of familial autonomic dysfunction in which a megacolon was present. In fact, the only gastrointestinal disturbances hitherto reported are attacks of cyclic vomiting. Riley[10] found such episodes in nearly two-thirds of his group. In view of the extensive autonomic innervation of the gastrointestinal tract it is perhaps surprising that so few alimentary disturbances have been found. Nevertheless, one wonders at the outset whether this megacolon is really part of the autonomic disorder or simply an unrelated coincidence.

In answering this question we kept in mind three general types of megacolon: psychogenic, anatomic, and neurogenic. The first, psychogenic group, seemed unlikely from the beginning. The patient's symptoms appeared when he was 3 months old, too early for such a complex emotional process. Entirely missing was the typical history of coercive toilet training, successful at first, followed later by regression. As the youngest child in an easy-going family of seven, the patient had been subjected to virtually no toilet-training efforts. Although he was emotionally labile, there was no evidence of gross social or personality maladjustment. The anatomic group includes a number of

kinds of megacolon: intrinsic or extrinsic obstructing tumors, anorectal stenosis, and stricture secondary to infection or surgery. Considerable time was spent searching for evidence of this category. Barium enema including flouroscopy and spot films clearly ruled out the presence of obstruction due to tumor. Careful rectal examination failed to show anal stricture of any kind and there was no history of surgery or rectal inflammation. Thus there was no evidence for any of the anatomic group. Most important of the neurogenic causes of megacolon is Hirschsprung's disease. In this disorder barium enema done by the Neuhauser technique characteristically outlines a narrowed segment of large bowel extending for varying distances above the anal sphincter. No such narrowing was observed in this case. In addition, the usual Hirschsprung's history was absent. The child did not sit straining at stool for long periods and did not produce thin, loose stools. Less common neurogenic megacolons are those associated with spina bifida and other spinal cord malformations. Neither these nor similar malformations were present.

The megacolon in this case could not be attributed to any cause outside the more general neurological disorder, familial autonomic dysfunction.

On the positive side, certainly no great reach of the imagination is necessary to see megacolon as a potential manifestation of the syndrome described by Riley (see Table I). The usual symptoms are motley: some sympathomimetic, some parasympathomimetic. They follow no pattern of hypo- or hyperfunction. Several of these varied features might conceivably contribute to megacolon. In the first place, these are loose, flaccid children with generalized muscular hypotonia. Should the abdominal muscles share this weakness, an important force in defecation would be lost. Moreover, some forms of sensation are diminished in this syndrome. Our patient paid no attention to repeated rectal examinations. Without proper appreciation of the normal signals to defecate, and with weak abdominal muscles, constipation and megacolon are plausible results. A third factor is suggested in a case reported by Day and Klingman.[2] A 6-year-old girl was studied because of acrocyanosis. She was found to have multiple neurological defects which were later recognized as those of familial autonomic dysfunction. When first seen she was a problem because of severe attacks of cyclic

TABLE I

| | PREVIOUS SERIES* (%) | OUR PATIENT |
|---|---|---|
| 1. Jewish family | 100 | 0 |
| 2. Deficient lacrimation | 100 | + |
| 3. Skin blotching | 97 | + |
| 4. Perspiration excess | 100 | + |
| 5. Drooling | 100 | + |
| 6. Emotional instability | 100 | + |
| 7. Motor incoordination | 100 | + |
| 8. Hyporeflexia | 97 | + |
| 9. Indifference to pain | 100 | + |
| 10. Hypertension | 85 | 0 |
| 11. Urinary frequency | 75 | 0 |
| 12. Pulmonary infections | 74 | 0 |
| 13. Breath holding in infancy | 73 | 0 |
| 14. Unexplained fever | 67 | 0 |
| 15. Cyclic vomiting | 63 | 0 |
| 16. Mental retardation | 55 | + |
| 17. Convulsions | 50 | 0 |
| 18. Corneal ulcers | 35 | 0 |
| 19. Small stature | + | + |
| 20. Poor speech | + | + |
| 21. Scoliosis | + | + |
| 22. Megacolon | - | + |

*From Riley,[10] based on a series of thirty-three cases.

vomiting in addition to the acrocyanosis. During one such vomiting attack a barium swallow showed complete pyloric obstruction. The block was apparently due to neurogenic spasm for it had entirely disappeared on a repeat film taken shortly after the attack. In our case such a neurogenic block, either prolonged or intermittant, may well add diminished peristalsis to weak muscles and poor sensation with megacolon in consequence.

As to the second unusual feature of this case—the lack of Jewish background—little need be said. Riley and co-workers[11] mention four non-Jewish children with some signs of dysautonomia. Of these, one was sufficiently tpical to be considered a full-blown case; the rest had only a few features and suggested a forme fruste of the disorder. Linde[6] has reported the only other typical case in a non-Jewish child.

Tracing our patient's family background, we find his mother's family to be French back at least four generations. His father's family had lived in Kentucky and Indiana for many generations. In neither line was there any evidence of Jewish ancestry.

Having discussed the unusual features of this case, it may be appropriate to add a few words about the relationship of familial autonomic dysfunction to a somewhat wider area of pathologic physiology. Much of this often vague territory is loosely marked off into clinical syndromes—the Ehlers-Danlos syndrome, congenital indifference to pain, acrocyanosis, and cerebral palsy, to name only a few. In this regard it is important to remember that giving a group of symptoms a name does not create a disease, separated forever from all others—even though, once named, we are fatally drawn to think of it as such. In fact, we shall see that in familial autonomic dysfunction we have a syndrome which acts centrifugally to bring together a number of apparently unrelated conditions. In doing so it emphasizes the importance of thinking in terms of pathologic processes rather than in terms of disease entities.

It is apparent that familial autonomic dysfunction is closely related to a number of diseases of the nervous system. Cerebral palsy is very similar in some respects. It too may be a diffuse disorder of the nervous system. Marmorization, poor coordination, and faulty speech are found in both. The syndrome of congenital indifference to pain may be the sole manifestation of autonomic dysfunction—indifference to pain being found in nearly 100 per cent of cases of the Riley-Day syndrome. Ford and Wilkins[4] described three children who had as an isolated (sic) neurological finding lack of appreciation of painful stimuli. The resemblance is heightened by the fact that in both conditions patients can tell sharp from dull, but do not respond quantitatively. In reviewing this original report by Ford and Wilkins it is significant to find that one of their patients showed attacks of high fever, vomiting, and abdominal pain, hypoactive reflexes, developmental retardation, and poor speech. This patient was very likely a case of the Riley-Day syndrome. Congenital pain absence is not the only syndrome to be distinguished by one of the features of familial autonomic dysfunc-

tion. Postural hypotension, bronchospasm, congenital hyperhidrosis, and absence of tears are considered by some as isolated entities. As mentioned earlier, the first case of autonomic dysfunction was reported by Day and Klingman as a case of acrocyanosis. In this syndrome the abnormality shared with Riley and associates is that of vasomotor control.

Familial autonomic dysfunction is a global syndrome touching systems besides the nervous system. In its effect on general growth it shares the characteristics of numerous large-scale trophic disorders. The loose hyperextensibility of ligaments and connective tissues mirrors one of the outstanding features of the Ehlers-Danlos syndrome.

Certainly the strongest resemblance to familial autonomic dysfunction is to be found in diencephalic epilepsy. Again we have a diffuse nervous system disorder with very similar symptoms. The earliest case was reported by Penfield[8] in 1929. A woman with paroxysms of autonomic phenomena was found to have an encapsulated tumor of the third ventricle pressing upon the thalamus. Engel and Aring[3] in 1945 described an 18-year-old boy with violent attacks of hyperthermia, abdominal pain and vomiting, fluctuating blood pressure, and asthma. It was incidentally noted that between attacks he drooled, did not produce tears when crying, had hyporeflexia, and was undersize. Though typical of familial autonomic dysfunction in many ways, the paroxysmal attacks of severe symptoms place the case partly in the category of cyclic disorders like epilepsy and migraine. At autopsy a cyst in the thalamus led these authors to postulate that the hypothalamus was released from higher (thalamic) control unleashing the seizures.

Finally Gibbs and Gibbs,[5] listing the symptoms of thalamic and hypothalamic epilepsy, include many characteristics of familial autonomic dysfunction. They described antisocial and vicious behavior, attacks of nausea and vomiting, and high temperatures. Their cases were marked electroencephalographically by 14 and 6 per second activity which they feel arises from the diencephalon.

It is here that we come closest to some glimpse of pathogenesis for in these cases we have cited evidence pointing more or less strongly to the thalamic-hypothalamic areas. With this in mind it is interesting to review the electroencephalogram record in our case. The most striking feature was evidence of diffusely abnormal electrical activity. In addition, however, 14 and 6 per second activity was found, very similar to that in the cases of hypothalamic epilepsy described by Gibbs and Gibbs. It tends again to focus our attention on the diencephalon.

In comparing familial autonomic dysfunction to these other syndromes we are involved in a simple process of classification—is it more like one or another. In this activity we are on historically respectable ground. Since the time of Linnaeus the classic first step in the search for causes has been to group phenomena which are alike, and separate those which are different. However, we have seen that incisive differences and exact similarities blur even as we watch them. The

best that we can do is point out the imprecisions and indicate the general terrain.

SUMMARY

A case of familial autonomic dysfunction in a non-Jewish 3-year-old white male child is presented. The clinical manifestation of megacolon in this patient is strikingly absent in previously reported cases. The similarities of this syndrome and others seem to reflect a diffuse disturbance of central nervous system function and perhaps other tissues as well. The relationship of familial autonomic dysfunction to a wide area of pathologic physiology is presented.

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# NONPARASITIC LIVER CYSTS IN CHILDREN

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NONPARASITIC liver cysts were first recorded in 1856, when Bristowe reported the occurrence of cystic disease in a 53-year-old shoemaker at post-mortem examination.[1] Since that time no more than 200 cases of "solitary" liver cysts have been reported.[2] Sonntag presented a classification which was modified by Jones[3] as follows:

A. Parasitic
   1. Echinococcal (hydatid)
B. Nonparasitic
   1. Solitary (simple: retention)
   2. Multiple (polycystic disease)
   3. Cystadenoma (proliferative)
   4. Pseudocyst (degenerative)
   5. Teratomatous (dermoid)
   6. Lymphatic (lymphangiomatous)
   7. Endothelial (ciliated epithelial)

The present study deals with solitary cysts of the liver occurring in children under the age of 13 years and stems from our recent experience with an infant at the Los Angeles Childrens Hospital. A search of the hospital records produced six additional cases, a significant finding when one considers the small number reported in the literature. Munroe,[1] in his excellent review, found only twenty-seven such cases in the pediatric age group, to which he added one. Poth and DeLoach[4] reported one and Hallenbeck and Fricke[5] two additional cases more recently.

Study performed at Childrens Hospital, Los Angeles, from the Department of Pediatrics, University of Southern California.

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## DIAGNOSIS

As in the cases reported herein, the diagnosis is usually made at operation or at autopsy, sometimes following a variable period of vague symptoms referable to the gastrointestinal tract. Abdominal distention is usually the first sign denoting an organic lesion. The principal reason for the relative absence of symptoms is the low internal pressure of these cysts in contrast to the high tension in parasitic cysts. This accounts for the frequent failure to palpate a well-defined mass on physical examination. In addition, low cyst tension permits progressive, gradual enlargement of the lesion without initial compression of adjacent viscera. Eventually, the space-occupying lesion displaces the more movable organs. It is this displacement as evidenced by contrast media radiologic studies which confirms the presence of the poorly defined abdominal mass. Roentgen studies further assist in differentiating these from echinococcus cysts by the absence of circular calcification of the cyst wall.[6, 7]

In our present series four of the seven cases occurred in males, in contrast to the reported preponderance in females.[8]

*Pathology.*—Characteristically, in addition to the low internal pressure,

the cysts may have loculations and may be 1 to 35 cm. in maximal dimension. The most common area of cyst origin is the anteroinferior surface of the right lobe of the liver. The direction of growth may be intra- or extrahepatic. The cyst fluid usually contains little or no bile, variable protein, some cholesterol, blood and its degenerative products, and debris.[1] Specific gravity and pH are too variable to be of differential significance. In the loculated areas the wall is thin, but in the thicker areas there are three fairly distinct fibrous connective tissue layers. Microscopically, the inner layer is richly cellular and may be lined with epithelial cells. The middle layer has predominantly collagenous fibers with few cells. In the intrahepatic portion the outer layer contains segments of bile ducts and islands of liver cells as well as the fibrous connective tissue framework which blends into the liver substance proper (Fig. 1). Hyalinization of the wall may occur in the extrahepatic portion. The absence of calcification microscopically is noteworthy.

The laboratory examinations are not characteristic and are of value only for exclusion of other conditions. Rarely does liver function impairment offer some clue to diagnosis.

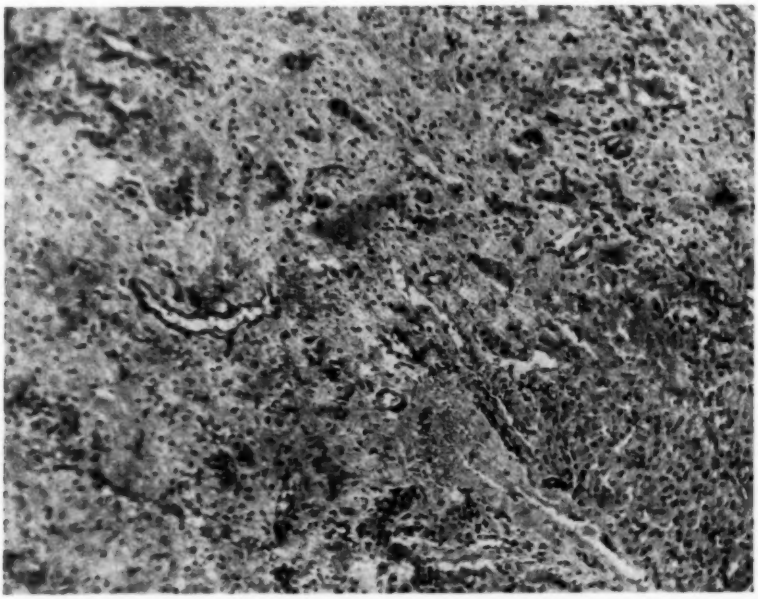

Fig. 1.—Microscopic section of intrahepatic portion of cyst wall, showing isolated hepatic cells both in nests and singly with compressed segments of bile ducts in a collagenous fibrous matrix. Case 1.

## INDICATIONS FOR SURGERY

Indications for surgery are divided into elective and emergency. The latter are less frequent but are related to possible trauma to the cyst with rupture, leakage, and peritoneal irritation. Also, intraluminal hemorrhage

with sudden enlargement and associated tenderness may be sufficient to warrant exploration. Most patients are operated upon electively, with no definite preoperative diagnosis. Recurrent vague abdominal symptoms lead to repeated finding of abdominal distention until complete studies, primarily roentgenographic, demonstrate a space-occupying lesion. Inability to exclude other varieties of tumor warrants abdominal exploration. Frequently considered differential diagnoses include hydrops of the gall bladder, choledochus cyst, polycystic disease, parasitic liver cyst, pancreatic cyst, hydronephrosis, mesenteric cyst, reduplication of bowel, and tuberculous peritonitis. Discussion of these entities is not pertinent here.

## CASE REPORTS

CASE 1.—R. A., a 2-year-old, white male, was admitted on Nov. 10, 1954, with a nine-month history of a protruding abdomen accompanied by transient, periorbital edema and enuresis. Hospitalization elsewhere showed no other abnormalities except an icterus index of 18 units. Nevertheless, hepatitis was offered as the working diagnosis, and a low-fat diet was prescribed. On the latter he lost 6 pounds. Shortly before admission to Childrens Hospital, polydipsia, polyuria, and dysuria with constipation were noted by the mother. The remaining history was noncontributory.

On physical examination the patient appeared well developed, well nourished, and not ill. The abdomen was protruberant with prominent superficial veins. There was no rigidity or tenderness. The liver edge could be palpated at the costal margin and was slightly rounded and nontender. There was a questionable, ill-defined, right-sided, cystic abdominal mass which appeared to be separate from the liver. The remaining examination showed only a reducible, complete, right inguinal hernia.

Repeat laboratory studies, including those of liver function, were normal except for a cephalin flocculation of 2 plus in twenty-four hours and 3 plus in forty-eight hours. Roentgenographic examinations included chest films, intravenous pyelograms, upper gastrointestinal studies, and barium enema. The right diaphragm was elevated and the right colon was displaced medially with no other abnormalities noted (Fig. 2).

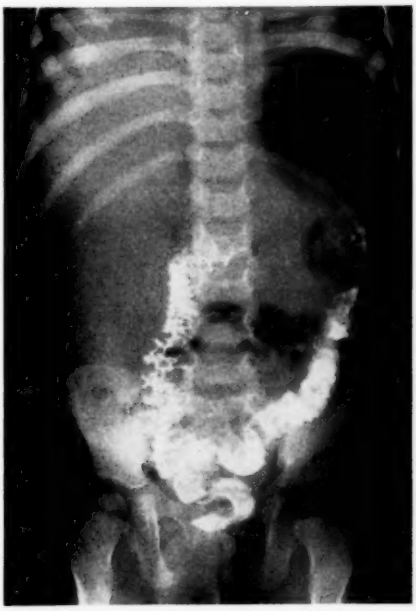

Fig. 2.—Postevacuation barium enema, showing medial and caudal displacement of the hepatic flexure by a homogeneous mass in the right upper quadrant. Case 1.

Abdominal exploration was performed on Nov. 29, 1954, and a large, solitary liver cyst was found which extended from the inferior surface of the right lobe of the liver down into the false pelvis. The mass was cone-shaped, with the apex inferior to the crest of the right ileum (Fig. 3). Maximal dimensions were 12 cm. by 20 cm. The surface was bosselated,

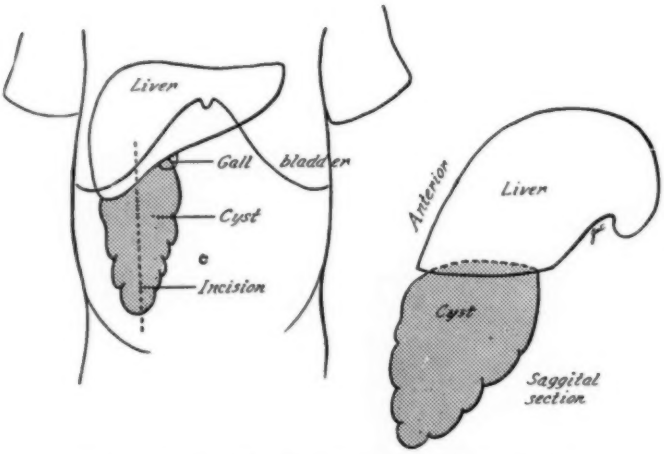


Fig. 3.—Diagram showing extent of liver cyst. Case 1.

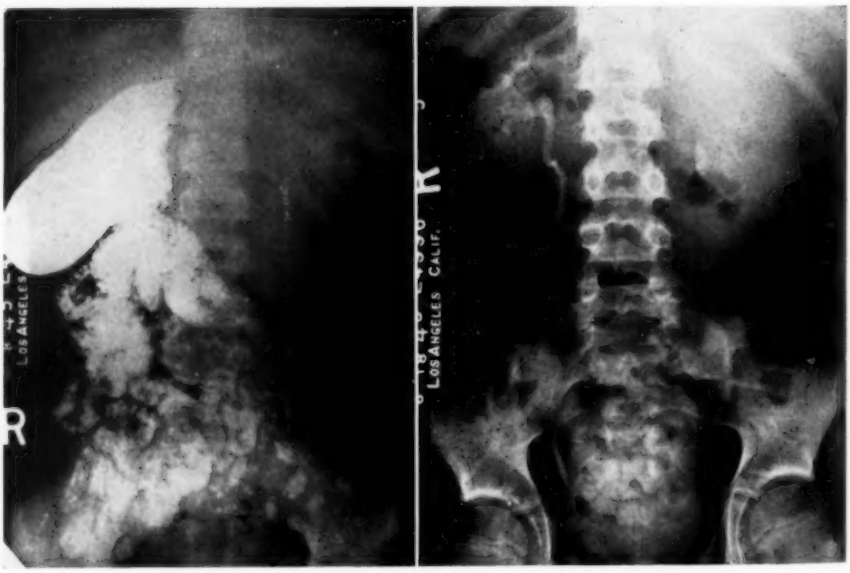


Fig. 4. Fig. 5.

Fig. 4.—Displacement of stomach to the right by a cyst. Case 2.
Fig. 5.—Pyelogram showing displacement of left kidney caudad by liver cyst. Case 2.

and through the transparent, thinner areas the yellowish, clear fluid content was visible. Low internal tension was demonstrated on palpation and incision for aspiration of the fluid. By sharp and blunt dissection, a plane was developed between the fibrous layers of the cyst wall in the intrahepatic portion. Considerable time was consumed and moderate blood lost in this maneuver, but enucleation was accomplished. The abdomen was closed with stab wound drainage. The cyst fluid did not contain bile on chemical examination.

The wall of the specimen was 2 mm. thick. On microscopic examination no definite lining was seen, but fibrous collagenous tissue with some hyalinization of the outer portion was prominent. Bile ducts and liver parenchymal cells were scattered in the mid-portion (Fig. 1).

The postoperative course was uncomplicated, the drains being removed on the eighth postoperative day and the patient discharged on Dec. 11, 1954. When last seen on May 8, 1955, he was asymptomatic.

CASE 2.—R. N., an 11-year-old, white male, was admitted on Aug. 7, 1945, with a history of left upper quadrant abdominal prominence of ten months' duration. The remaining history was noncontributory.

On physical examination an abdominal mass was palpated which filled the left upper quadrant. There was no tenderness or rigidity of the abdomen. No other organs or masses were palpable. Laboratory studies were within normal ranges. A density in the left upper quadrant resembling the spleen was noted in the roentgen films. The stomach was displaced to the right on upper gastrointestinal roentgen study (Fig. 4). Intravenous pyelograms showed the left kidney pushed caudad and slightly lateral (Fig. 5). On Aug. 22, 1945, marsupialization and iodoform packing of a large, solitary cyst on the inferior surface of the left lobe of the liver was performed with biopsy of the cyst wall. The cyst contained an estimated 2 liters of clear, yellowish fluid, and the inner surface of the wall was trabeculated. The remaining organs were normal. The postoperative course was uneventful. On Aug. 19, 1953, at 19 years of age, the patient was still asymptomatic and physical examination was normal.

CASE 3.—T. R., a 7½-year-old, white female, was admitted on Dec. 9, 1953. Four weeks prior to admission she had a skating collision during which another girl fell across her abdomen. The mother noted that the patient was white and clammy for two hours. Thereafter, she complained of intermittent, right upper quadrant abdominal ache, which lasted less than a half hour, about twice a day and which was relieved by splinting the right side. One week later the mother noted a right upper quadrant swelling and, on the following day, dark clots and a red streak of blood in one stool. The patient was hospitalized elsewhere. Roentgenograms, blood and stool examinations, and cystoscopy were performed, but the nature of the upper quadrant mass was not apparent. No jaundice, acholic stools, or dark urine were noted. The mass seemed to vary in size. The remaining history was noncontributory.

Physical examination showed a prominence of the right lower rib cage. There was a visible and palpable right upper quadrant abdominal bulge, 14 cm. by 19 cm., which was firm but cystic and immobile. It was felt to overlie and be part of an enlarged liver, the lower edge of which was sharp, nontender, and 9 cm. below the right costal margin down to the level of the umbilicus.

Laboratory studies, including those of liver function, were normal except for the Bromsulphalein test which showed 32 per cent dye retention in thirty minutes and 38 per cent in sixty minutes. The cephalin flocculation was 1 plus in twenty-four hours and 2 plus in forty-eight hours. Roentgen studies included a negative chest film. A flat film of the abdomen

showed a huge, homogeneous zone of increased density to either side of the midline related to the liver. The stomach was displaced somewhat to the left and posteriorly. There was no calcification. On Dec. 11, 1953, an exploratory abdominal laparotomy was performed. A cyst in the right lobe of the liver was found which measured about 25 cm. in diameter. The gall bladder and bile ducts appeared normal. The cyst contained about 800 c.c. of cloudy, viscid, bile-stained fluid,

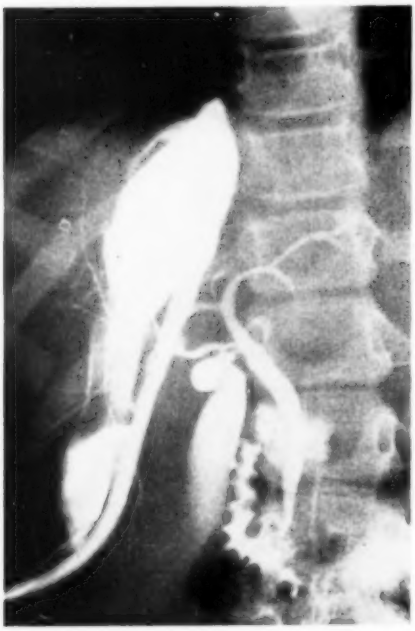

Fig. 6.—Retrograde opaque media studies through catheter draining liver cyst, showing continuity with the biliary tree. Case 3.

which was aspirated. The cyst was drained via a No. 16 Robinson catheter brought out through a stab wound. A liver biopsy showed the portal areas to be prominent due to the presence of fibrous tissue reaction, lymphocytes, and bile duct proliferation. A small section from the cyst wall showed dense fibrous reaction in which yellow-stained pigment was noted. There were lymphocytic and monocytic infiltration and evidence of fibrous tissue reaction with bile duct proliferation in one area. The postoperative course was uncomplicated. On the eleventh postoperative day, a Bromsulphalein test was repeated and found to be normal. The following day Diodrast was injected into the cyst through the catheter, which by now was draining a minimal amount of thin, yellow fluid. The dye filled a large, ovoid chamber, 5 cm. by 7 cm. in diameter, in the right lobe of the liver, and the column passed readily throughout the biliary tree and into the duodenum (Fig. 6). Before complete removal of the catheter, retrograde dye studies showed that the cyst cavity had become completely obliterated. The patient was discharged on Dec. 30, 1953. There was no drainage one month after operation and she was asymptomatic when seen ten months postoperatively.

The remaining four cases had nonparasitic liver cysts found incidentally at autopsy.

Case 4.—D. B., a 3-day-old, premature female infant with bronchopneumonia and internal hydrocephalus, was admitted on Jan. 1, 1944. The patient died at the age of 2½ months, and at autopsy a solitary, 1 cm., round cyst was found on the anterolateral surface of the right lobe of the liver. Microscopic section showed a thick layer of dense fibrous tissue in the cyst wall with occasional islands of liver cells. No other cysts in the liver or other organs were noted.

Case 5.—M. D., a 4½-year-old, white male, had lymphocytic leukemia with symptoms for four months. At autopsy the liver was enlarged twice normal size, and a cyst, 2 cm. in diameter, lay on the anterior surface. Microscopic findings showed a lymphocytic, leukemic infiltrate. The cyst was filled with acellular, granular, pink material and was lined with roughly cuboidal, ciliated epithelium.

Case 6.—B. B., a male patient, was admitted shortly after birth because of

a large omphalocele containing liver and intestine. He underwent surgery at the age of one day for repair of the omphalocele and died shortly thereafter. Autopsy findings included congenital heart disease, incomplete rotation of the mesentery of the small and large intestine, and a subcapsular hematoma in the left lobe of the liver. Two gross cysts in the parenchyma of the right lobe near the periphery, 2 cm. and 1 cm. in diameter, contained yellow, watery fluid and were lined by a thin, smooth, slightly opaque membrane. Microscopically, there were several other cysts of varying sizes. The lining was composed of low columnar or cuboidal epithelium containing abundant cytoplasm and large pale nuclei.

CASE 7.—J. T., a 3-day-old, female patient, was admitted because of a large omphalocele containing liver, spleen, stomach, and intestines. She was operated upon within a few hours after admission and died postoperatively. At autopsy there were findings of congenital heart disease, marked atelectasis, and three liver cysts, measuring 2 mm. to 5 mm. in diameter, in the subcapsular parenchyma of the right lobe. These were lined by a single layer of cuboidal epithelium.

## SURGICAL TREATMENT

The finding of solitary, nonparasitic liver cysts at surgical exploration has resulted in several modes of management. Where feasible, with the patient in good condition and the mass sufficiently extrahepatic, a cleavage plane is developed in the cyst wall near the attachment to the liver. This allows for enucleation of the entire cyst except for the outer part of the wall adjacent to the liver parenchyma; the rim of this remnant lends itself to oversewing, thus obliterating the raw surface in the cyst bed. This method has been employed in one patient herein reported (R. A.) and by other authors.[4, 9-11] It seems preferable to any other method, if the cleavage plane can be developed without excessive blood loss or operative time that would add to the morbidity or mortality.

Another method employed is marsupialization with or without partial excision as used in patient R. N. reported here and in other patients in the literature.[1, 12] Less operative risk is involved in this method, but there occurs prolonged postoperative drainage from weeks to years.[8] In some instances a variety of agents have been employed in attempts to obliterate the remaining cavity and stop drainage. Zenker's solution,[1] silver nitrate,[12] Carnoy's solution,[13] phenol, alcohol, tincture of iodine, and iodoform gauze have been used. These agents also may follow another method of management, namely, simple drainage, as in our Case 3 and in the literature.[11, 14] Where speed is mandatory, this method would seem most desirable.

Some noteworthy features in surgical management are mentioned by various authors. The surgical mortality rate has been reported to be between 10 and 32 per cent. Death has resulted from shock induced by sudden release of fluid content from a large cyst.[15, 16] In some instances where cysts are drained with or without marsupialization, surprisingly rapid spontaneous obliteration has occurred. Actual continuity with the biliary tree has been demonstrated (patient T. R.) by retrograde injection of radiopaque substance into the draining cyst space.

## DISCUSSION

The occurrence of nonparasitic liver cysts, not associated with polycystic disease, in the very young patient

would infer a congenital origin (hamartoma).[10] In one reported instance a large, solitary liver cyst in the fetus interferred with delivery.[1] Again, both minute and large cysts occur in the newborn infant, occasionally coincident with other congenital defects.[17, 18] In two instances of omphalocele, liver cysts were found at the autopsy table, indicating a possible relationship (Cases 6 and 7). Trauma is reported to cause "pseudocysts," so called because of the absence of a lining endothelium.[4, 5] This may have been the situation in Case 3. Large cysts have been reported without such a lining, however, and not associated with trauma.[18, 19] Cysts increase in size, probably by coalescence, internal tension, external trauma, transudation of fluid, or actual cellular reproduction. The clinician sees perhaps half of the proved cases and then only when a sufficiently large size is attained to produce suggestive symptoms or signs. Then, a complete investigation is undertaken with the radiologist playing an important part in proving the existence of a strange mass which displaces the abdominal viscera. In the absence of a definite diagnosis, surgical exploration is indicated. It is our opinion that were the precise diagnosis made, surgical treatment would still be indicated, since shock and death have occurred from sudden operative drainage[19] as could happen with accidental rupture of a large, solitary cyst.

## SUMMARY AND CONCLUSIONS

The rare entity of solitary nonparasitic liver cysts in children has been described. Three operated and four incidental autopsy cases are reported. The various theories of origin have been mentioned. The difficulty in preoperative diagnosis and the necessity for surgical exploration are emphasized. The various methods of surgical treatment and their preferential use are discussed. Surgery is concluded to be the only appropriate treatment with enucleation or extirpation being the most desirable, where feasible.

We are indebted to Drs. M. E. Greaney, F. Leix, and W. J. Norris for the use of their patients in this report; to Dr. M. J. Carson of the Pediatrics Department and Dr. W. C. Thomas of the Pathology Department, Childrens Hospital, Los Angeles, California, for their valuable suggestions; and to Misses J. Fink and N. Teaford for help in preparation of the manuscript.

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## Addendum

Since this report was submitted, one other case of nonparasitic cyst of the liver was seen. It is briefly described.

D. M. H., a 5½-month-old white female, was admitted on April 21, 1956, with progressive enlargement of the abdomen for two and one-half months and signs of a fecal impaction for one day. On examination the abdomen was distended and an irregular firm cystic mass was palpable over the entire right half of the abdomen. Roentgen studies confirmed the presence of a mass displacing intestine and the right kidney. At surgery on April 25, 1956, Dr. J. N. Nichols removed part of a multiloculated liver cyst containing one liter of clear fluid. Difficulty in dissecting the portion of the cyst wall adherent to the liver precluded its complete removal. From the twelfth to the fifty-first postoperative day, the wound drained purulent material of varying amounts while the patient ran a sporadic "septie" fever. A resistant staphylococcus and pseudomonas infection in the wound gradually responded to a variety of combinations of antibiotics and local irrigation of the wound.

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*Of Crooked and Lame Children*

It hapneth that a Child is born with crooked feet, placed and pressed one upon another, and must go on the ancles if they can; they usually say, that such lame births are caused by frights, strange sights, or by carelessness, which also Nurses have to answer for. These defects they say usually are incurable; it agreeth with that saying, no body maketh himself crooked. These idle pratings causeth and lazy people, pretending, if my lame Child cannot be cured, why should I be at expences or taking of pains. It is a base and false excuse, because experience proveth it to be otherwise. To liken this to an example, may have eaten from that Trees fruit, which they nursed by putting the kernell into the ground; my self have eaten the fruit of a Tree, six years after I put the kernel thereof into the ground. Even so is it with lame Children, somewhereof I cured so, that after some yeers I saw them go straight. Let no man be neglective if his Child be thus crooked, as not to ask counsel about it; though all be not recovered which are in such cases, yet many are cured and if not perfectly, yet may they be mended in some sort; the which I do demonstrate with examples. I have dressed a new born Child, and ordered it with splinters as I thought fitting, whose feet from his Mothers wombe stood so, that the Child stood on the outside ancle, which with splinters I brought to right, and that Child went as straight as any other.

—From Felix Würtz, 1565.

# PURPURA IN CHILDHOOD

## Observations in 187 Cases

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PURPURA is encountered frequently in practice. It is especially prevalent among children and younger adults. "Purpura" is a descriptive term and by no means a diagnosis, since it is the accompaniment of many and varied illnesses. It is the task of the physician to discover the cause underlying the purpura if possible, in order to treat the patient successfully.

Fundamentally, all purpura is related to two defects: one is in the smallest blood vessels and permits the loss of blood from these vessels into the surrounding tissues with visible hemorrhage, and the other is in the blood itself either as a deficiency of platelets or as an abnormality in those elements of the blood serum concerned with clotting. Finally, disturbances in the globulin fraction of the blood as noted in the collagen disorders may be associated with purpuric manifestations.

### CLASSIFICATION OF PURPURA

Of the many classifications of purpura, perhaps the simplest and most useful one is that made up of two broad categories; namely, thrombopenic purpura, in which the number of platelets in the blood is decreased, and nonthrombopenic purpura, in which the number of blood platelets is normal. Thrombopenic purpura may be idiopathic or secondary to other conditions or agents such as infections or drugs and chemicals. Idiopathic thrombopenic purpura may be either acute (duration of two months or less) or chronic; splenectomy seems to be a more reasonable procedure for the chronic form than for the acute form. Nonthrombopenic purpura may be anaphylactoid or allergic in nature, with involvement of the joints, intestinal mucosa or kidneys in association with the purpuric lesions of the skin, or it may be secondary to other conditions as noted above in the thrombopenic varieties.

Since the appearance of excellent reviews of the subject of purpura in children by Newton and Zuelzer[1] and by Clement and Diamond,[2] my colleagues and I have been interested in analyzing our own experience in view of the fact that our tendency has been to treat more of the patients surgically than did the authors mentioned. Hence, the records of 187 infants and children less than 15 years of age who had purpura of different types and who were seen at the Mayo Clinic in the decade 1945 through 1954 were reviewed. The observations made in this review form the basis of this paper.

From the Section of Pediatrics, Mayo Clinic and Mayo Foundation.

### DISTRIBUTION OF CASES ACCORDING TO YEAR, AGE, AND SEX

The total of 187 patients for the ten-year period represents an average of almost nineteen cases a year. The annual number of cases tended to increase during the decade.

Most of the patients were in the younger age groups, more than half being 6 years of age or less. Six were less than 1 year of age, and three of these had purpuric lesions of the skin at birth. There were almost equal numbers in the age groups 1 through 4 and 5 through 9 years, and only about one-half as many in the age group 10 through 14 years as in each of the two preceding age groups.

The distribution of cases according to sex varied little with age or with type of purpura. This sex distribution is contrary to the situation in adults, in which females significantly outnumber males. In fact, in the ages less than 10 years males were affected slightly more frequently than were females. In the age group 10 through 14 years, the reverse, or the accepted adult preponderance of females over males, was noted.

### ANALYSIS OF CASES ACCORDING TO TYPE OF PURPURA

Of the 187 patients in this series, 105 had thrombopenic purpura and 82 had nonthrombopenic purpura (Table I). The number of cases of the thrombopenic form encountered each year usually exceeded the number of cases of the nonthrombopenic form; in only two of the 10 years was the reverse true. As pointed out by Clement and Diamond,[2] such a difference does not indicate the probable relative frequency of these two types of purpura in children as it is encountered in general practice, but rather it reflects the increased number of patients that were referred for study because they presented difficult problems of bleeding and because they might require splenectomy.

TABLE I. PURPURA IN CHILDHOOD: DISTRIBUTION OF CASES ACCORDING TO TYPE OF PURPURA, 1945 THROUGH 1954

| | | CASES | |
|---|---|---|---|
| Thrombopenic purpura | | | 105 |
| Idiopathic | | 78 | |
| Acute (2 mo. or less) | 26 | | |
| Chronic | 52 | | |
| Secondary | | 27 | |
| Infection | 24 | | |
| Involvement of bone marrow | 3 | | |
| Nonthrombopenic purpura | | | 82 |
| Anaphylactoid | | 49 | |
| Secondary | | 33 | |
| Infection | 18 | | |
| Other causes | 15 | | |
| Total | | | 187 |

*Thrombopenic Purpura.*—In approximately one-fourth of the 105 cases of thrombopenic purpura the condition was secondary to infection, and in three-fourths it was idiopathic, that is, there was no evident cause for the bleeding, such as drug reactions, vitamin C or K deficiency, or underlying blood dyscrasia such as leukemia or aplastic anemia.

About one-fourth of the 105 cases of thrombopenic purpura were of the acute idiopathic type and about one-half were of the chronic idiopathic type. In the remaining one-fourth, the purpura was secondary to the acute exanthemas or to acute respiratory infections. In three additional patients the purpura was secondary to involvement of the bone marrow by x-ray irradiation in one case, by drug intoxication in one case, and by reticuloendotheliosis in one.

Two infants had purpuric lesions of the skin at birth, the lesions in both being due to sepsis, and a third had a history of purpura that had occurred after birth and that had persisted until the age of 13 months. Other members of the third child's family tended to bruise easily. Transplacental passage of platelet agglutinins, similar to passage of agglutinins that cause sensitization of red cells of the infant in erythroblastosis fetalis, or platelet incompatibility between mother and child may have been at fault. All three infants were severely thrombopenic and one died of sepsis.

*Nonthrombopenic Purpura.*—Of the eighty-two patients who had nonthrombopenic purpura, forty-nine had the so-called anaphylactoid or allergic type, which is believed to be due to capillary damage by drugs or by allergens that usually are bacterial in nature and result from recent infection. All of these patients had bleeding into the skin and usually into the oral or nasal membranes; this has been called "purpura simplex" (Table II). Next in frequency was the type in which, in addition to involvement of the skin, the joints are affected, with effusion and pain; this is known as Schönlein's purpura. Still less frequent was Henoch's purpura, with visceral bleeding that usually is manifested by melena or hematemesis. Eighteen patients with the anaphylactoid type of purpura had hematuria with albuminuria and, at times, azotemia and hypertension, so that vascular damage in the kidneys was suspected. Indeed, there are those who hold that the distinction between this condition and the collagen disorders of rheumatic fever, disseminated lupus, and periarteritis is difficult to make.[3, 4]

TABLE II. NONTHROMBOPENIC PURPURA IN CHILDHOOD: DISTRIBUTION OF CASES ACCORDING TO TYPES, 1945 THROUGH 1954

| | CASES |
|---|---|
| Anaphylactoid (Schönlein-Henoch) | |
| Purpura simplex (skin only) | 49 |
| Purpura rheumatica (skin and joints) | 36 |
| Purpura abdominalis (skin and viscera) | 30 |
| Hematuria | 18 |
| Secondary | |
| Acute infection (exanthematous, respiratory) | 17 |
| Vascular defect (mechanical, orthostatic) | 13 |
| Chronic disease (nephritis, cirrhosis) | 1 |
| Drugs and chemicals | 1 |
| Congenital thrombasthenia | 1 |

Besides the patients with anaphylactoid purpura, there were eighteen who had bleeding into the skin during the course of or following an infection. Platelet counts were normal. The bleeding in these cases could be considered a skin-sensitization phenomenon, and hence these cases might reasonably be added to those of anaphylactoid purpura. The infections usually were of the respiratory tract or of the contagious variety, although one was classified as chronic nephritis and toxic hepatitis–conditions which purpura may accompany. In the remaining cases of nonthrombopenic purpura, the purpura was classed as vascular and not due to any discernible allergic mechanism in ten, as factitial in two, as orthostatic in one, and as congenital thrombasthenia in one; in an additional patient there seemed to be clear-cut evidence of purpura caused by a drug. None of these patients had a lack of platelets or a demonstrable defect of clotting. An allergic background was not a prominent

finding in the histories of patients with either type of nonthrombopenic purpura, and sensitivity to drugs was infrequently noted despite the widespread use of chemotherapeutic and antibiotic agents.

*General Clinical Appearance.*—The clinical picture in all the cases varied with the location and extent of the bleeding. Many children were surprisingly comfortable despite widespread purpura. Fever was noted only in the most severely ill patients and was not unusually high unless associated with infection. Pallor was usually absent unless there had been severe bleeding.

### SPLENOMEGALY

A palpable spleen was mentioned in the records of the physical examination of twenty-one of the patients with thrombopenic and ten with nonthrombopenic purpura. In only nine was the enlargement recorded as being of significant degree. However, more than one-half of the spleens encountered at splenectomy were significantly overweight for the age and size of the patient. There was no constant or diagnostic pattern in the reports of the pathologists on the spleens removed. When splenomegaly is a prominent feature on physical examination, one should look further for diagnostic possibilities, as great enlargement of the spleen is not characteristic of purpura of any type; such enlargement may indicate congestive splenomegaly or splenomegaly due to a primary blood dyscrasia.

### COMPLICATIONS

Intracranial bleeding is a dreaded complication in purpura; it occurred in five patients of this series, in two of whom it developed in the course of acute thrombopenic purpura and the patients died before treatment could be instituted. Two of the five patients came with evidence of previous cerebral hemorrhage; one of these was left with blindness in one eye, the other with a severe mental defect. The fifth patient died at home of cerebral hemorrhage that resulted from deficiency of platelets and aplasia of the bone marrow due to drug intoxication. All of these children had purpura of the thrombopenic type.

Menorrhagia was noted in five adolescents and vaginal bleeding was noted in three younger girls. The bleeding in one patient was sufficient to require hysterectomy after splenectomy had failed to stop it. All of these patients had thrombopenic purpura.

Hematuria has been mentioned as occurring frequently in anaphylactoid purpura. Eighteen patients in this series were so affected. An additional seven patients in the thrombopenic group had hematuria. In many cases the hematuria was slow to clear up, although in only one instance did it go on to chronic nephritis. This was in a child with anaphylactoid purpura. This aspect of purpura has been dealt with in detail in recent publications.[2, 5, 6] Our experience has been more favorable than that reported by others.

### LABORATORY OBSERVATIONS

Laboratory studies help to differentiate the types of purpura clearly (Table III). In the present series of cases, the concentration of hemoglobin and the erythrocyte count were usually normal or decreased, depending on the

amount of blood lost. The leukocyte count was normal, or increased in the presence of infection. The data supplied by examination of blood smears were important in the elimination of other causes of purpura, such as leukemia and aplastic anemia. Eosinophilia was noted in both types of purpura, although it was not striking. Platelets were few or absent in thrombopenic purpura, whereas they were present in normal numbers in nonthrombopenic purpura. The erythroid and leukocyte series were normal.

The bone marrow of eighty-three patients was examined. This number includes all patients subjected to splenectomy, and it includes almost all patients in the thrombopenic group and several in the nonthrombopenic group in whom the underlying cause of the purpura was in doubt. Thus, one would rule out the presence of leukemia, aplastic anemia, malignant involvement of the bone marrow by metastasis, and granulomatous disease. The megakaryocytes were almost universally present in normal numbers but were not splitting off platelets in normal fashion. Eosinophilia of the bone marrow, which has been suggested as a good prognostic omen, was noted occasionally.

The platelet count was definitely less than normal in thrombopenic types of purpura; usually it was less than 50,000 per cubic millimeter of blood (normal range: 100,000 to 250,000). As this is a difficult laboratory procedure to carry out accurately, a succession of platelet counts is advisable to establish a base line. There was poor correlation between the platelet count and the tendency to bleed. Of the children with thrombopenic purpura, many whose platelet count was maintained at less than 30,000 did not bleed, whereas others whose count was maintained at a higher level did bleed. Immediately after splenectomy the platelet count usually rose precipitously; less often the rise was delayed, and in the patients with a poor outlook there was no rise in the count. No rise oc-

TABLE III. PURPURA IN CHILDHOOD: LABORATORY TESTS

| | PURPURA | |
|---|---|---|
| | NONTHROMBOPENIC | THROMBOPENIC |
| Hemoglobin, erythrocytes | Normal | Normal or decreased |
| Leukocytes | Normal or increased | Normal or increased |
| Platelets | Normal | Low |
| Blood smear | Normal | Platelets low |
| Bone marrow | Normal | Megakaryocytes: Normal number but abnormal function |
| Bleeding time | Normal | Prolonged |
| Clot retraction | Normal | Prolonged |
| Coagulation time | Normal | Normal |
| Urine | Albumin, erythrocytes ± | Erythrocytes ± |
| Tourniquet test | Negative | Positive |

curred in eight cases, with three deaths. In spite of rises in the platelet count to more than 1,000,000, thrombotic phenomena were never encountered nor was anticoagulant therapy found necessary.

Prolongation of bleeding time occurs in patients with low platelet counts and is characteristic of thrombopenic purpura. The bleeding time was often longer than thirty minutes in the present series of patients, and the clot retraction time was more than twenty-four hours in many instances, which is a corollary to the lack of platelets. The coagulation time was always normal in both categories of purpura and served to rule out hemophilia. The Rumpel-Leede phenomenon, or cuff test, was positive in many of the thrombopenic patients and in a few of the nonthrombopenic patients. This is a measure of capillary fragility, which correlates better with the patient's tendency to bleed than does the platelet count.

As mentioned previously, hematuria occurred in seven patients with thrombopenic purpura and in eighteen patients with anaphylactoid or nonthrombopenic purpura. Albumin was present when the degree of hematuria was moderate to severe. For the series as a whole, abnormalities of the urine were infrequent but were present often enough to indicate that they should be sought.

### PROGNOSIS

The prognosis for all types of purpura in children is good. Recent reports on this subject by Newton and Zuelzer,[1] by Clement and Diamond,[2] and by Komrower and Watson[7] indicate that purpura is a self-limited disease in children and has a favorable outlook without splenectomy in the majority of cases.

There were eleven fatalities in the present group of 187 cases. All deaths were in the thrombopenic category, and seven of these were in the group in which the purpura was related to secondary factors. Three of these seven patients died of the toxic effects of x-rays or drugs on the bone marrow, one of toxoplasmosis, one of meningococcemia with adrenal hemorrhage, one of sepsis and intestinal obstruction, and one of toxic hepatitis and nephritis. There were four deaths in the idiopathic thrombopenic group. Three of these patients had acute purpura, of whom one had generalized and fulminating hemorrhage and the other two had sudden, fatal, cerebral hemorrhage; the fourth, a 14-year-old girl, had chronic idiopathic purpura and died of uncontrolled menorrhagia.

### TREATMENT

In the secondary types of purpura, either thrombopenic or nonthrombopenic, the underlying condition should be sought out and treated. The offending drug or chemical is removed or the infection is discovered and treated appropriately. Blood lost is replaced with fresh whole blood to furnish the maximal supply of healthy platelets, which are said to last normally for four to six days after transfusion. Transfusion of platelets has been advocated but this may be disappointing, since the patient may become sensitized so that a subsequent transfusion is of decreasing value as a means of supplying viable platelets. By the silicone technique, platelets

may be preserved from damage in delivery to the patient.

*Hormonal Therapy.*—Treatment with steroid hormones is considered helpful in controlling bleeding, although the mechanism by which they act is not clear. An intravenous drip of corticotropin (ACTH) in glucose or isotonic saline solution in doses of 25 to 40 mg. daily over a period of eight to twelve hours may be lifesaving when bleeding is acute and severe. These agents are also useful in the preparation of the patient for splenectomy. My colleagues and I have observed the effect of steroid hormones on twenty-seven children with purpura during the period of this study, eighteen of whom had the thrombopenic type and nine the nonthrombopenic variety of purpura. All received cortisone except five who were given corticotropin. Dosage varied with the form of hormone employed and the size of the child. For cortisone, the dose ranged from 50 to 200 mg. a day; for corticotropin, from 20 to 40 mg. a day. It was not possible to obtain accurate data on dosage for five of the children treated elsewhere. A review of the records of our own patients treated in the manner described indicates that the doses used may have been small in the light of present-day knowledge. None of our patients with nonthrombopenic purpura showed improvement under this form of therapy.

All but four of our patients with thrombopenic purpura who were treated with steroid hormones finally underwent splenectomy with good results except for an 11-year-old boy who had fulminating purpura and who died of uncontrolled, generalized bleeding. Three patients continued with subnormal platelet counts for several months following splenectomy but they were clinically well. No instance of therapy with these hormones for longer than three weeks was noted, and two children were treated for periods that were too short to permit evaluation, since splenectomy was carried out shortly after therapy with steroid hormones was started. Of the children with thrombopenic purpura who were treated with hormones but who were not splenectomized, one recovered after cortisone treatment and was well two years afterward, one is unimproved, one died of a cerebral hemorrhage on the fifth day of corticotropin therapy, and the fourth is untraced. We failed to note the beneficial effect on the bleeding tendency reported by others.[8-11]

It is possible that larger doses of either hormone should be employed in handling these patients and used for longer periods in order to control bleeding. Results may be complicated by the appearance of hypercortisonism. The use of the newer preparations such as Prednisone may avoid the unfavorable effects of therapy with cortisone or corticotropin.

*Splenectomy.*—When bleeding has been severe or prolonged, splenectomy has been our treatment of choice. Because of our experience with fatal bleeding in three children with acute idiopathic purpura, it has not been apparent to us that, without resort to surgical measures, the prognosis for children with purpura of this variety is better than it is for adults. Why removal of the spleen is helpful in this condition is not at all clear today even though the procedure

has been done repeatedly since it was first suggested in 1916 by Kaznelson. The theories advanced for the beneficial results of splenectomy are on the basis of (1) excessive destruction of platelets in the spleen, (2) elaboration, by the spleen, of a humoral substance that depresses formation of platelets in the marrow, and (3) removal of a source of antibody production resulting from an unknown stimulus.

As cited previously, there is evidence in the literature that acute thrombopenic purpura and nonthrombopenic purpura subside spontaneously in children.[1, 2, 7] This is in contrast to the reported results of surgical versus medical treatment of patients of all ages combined; these reports indicate that splenectomy gives good to excellent results in three-fourths of the patients so treated, whereas medical treatment gives similar results in only one-third of the patients so treated.[12] In a previous report from the Mayo Clinic it was said that a good response to splenectomy occurred in 85 per cent of fifty-nine adults and in 90 per cent of twenty children.[13] In the present series of 105 patients with thrombopenic purpura in children, fifty-four underwent splenectomy for purpura of the idiopathic thrombopenic variety. Of these, fourteen had acute purpura (less than two months in duration before splenectomy) and forty had chronic recurring purpura. In the latter the duration before splenectomy was two to six months in twelve patients, six to twelve months in ten, and one to eight years in eighteen; the median duration was ten months. In the period represented by these cases (1945 through 1954), the percentage of patients with thrombopenic purpura who underwent splenectomy tended to decrease in the later years of the period as compared with the earlier years, and the ratio of patients with acute thrombopenic purpura who underwent splenectomy to the total number with thrombopenic purpura also tended to diminish during this time. Ten patients in the series underwent splenectomy elsewhere—six before coming to the clinic and four after dismissal. Follow-up information obtained on fifty patients one to ten years after operation indicates that thirty-seven were well and eight had experienced improvement; thus, 90 per cent of the traced patients were benefited. The condition of three was unimproved and two had died in the postoperative period (Table IV). In the group of patients with idiopathic thrombopenic purpura treated nonsurgically, fifteen were well, one improved, one unimproved, and two were dead of their disease; thus, 84 per cent of the traced patients were benefited by medical treatment.

The favorable effect of splenectomy on the platelet response is shown in Table V.

Of the two fatalities from splenectomy, one was that of an 11-year-old boy with a two-day history of severe bleeding from the nose and with generalized purpura. His platelets numbered 33,000 and the appearance of the blood smear and the bone marrow was consistent with a diagnosis of acute idiopathic thrombopenic purpura. He was treated with cortisone, 100 mg. daily, for two days, and then splenectomy was performed. Despite transfusion of 2,000 c.c. of fresh blood, he continued to bleed and

died one day postoperatively. Postmortem examination disclosed 3,000 c.c. of blood in the peritoneal cavity and small bowel. The splenic pedicle was intact. No cause was found to explain the bleeding tendency.

The other fatality was that of a 14-year-old girl who had had severe menorrhagia for five months and purpuric spots in the skin which had followed an attack of measles. The platelets numbered 46,000 and she was moderately anemic. Examination of peripheral blood smears and the bone marrow did not disclose any evidence of leukemia but it did disclose decreased platelet formation in a hypocellular marrow. Splenectomy was finally carried out after treatment with fresh whole blood and cortisone, 200 mg. daily for eight days, had been ineffective and the situation looked desperate. The girl continued to bleed into the skin and from the uterus and died eight days postoperatively. A large intraperitoneal hemorrhage was found at post-mortem examination. The splenic pedicle was intact. The pathologist was unable to find a cause for the bleeding.

These two fatalities among fifty-four children who underwent splenectomy represent a mortality rate of less than 4 per cent, which does not seem excessive in view of the severity and chronicity of the illness in many patients.

The indications used for splenectomy in idiopathic thrombopenic purpura have been (1) prolonged or severe bleeding unresponsive to other measures, (2) severe menorrhagia in young girls near or in adolescence, and (3) recurring purpuric episodes of a degree or length that limit the activities of a child of that age because of the danger from trauma. Splenectomy has been considered to be contraindicated in (1) nonthrombopenic purpura, (2) symptomatic or secondary purpura, and (3) purpura whose nature is not clear.

TABLE IV. RESULTS OF TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDREN, 1945 THROUGH 1954

| RESULT | SPLENECTOMY | | MEDICAL TREATMENT | |
|---|---|---|---|---|
| | ACUTE | CHRONIC | ACUTE | CHRONIC |
| Well | 12 | 25 | 9 | 6 |
| Improved | — | 8 | — | 1 |
| Unimproved | — | 3 | — | 1 |
| Dead | 1 | 1 | 2 | — |
| Untraced | 1 | 3 | 1 | 4 |
| Total | 14 | 40 | 12 | 12 |

TABLE V. PURPURA IN CHILDHOOD: EFFECT OF SPLENECTOMY ON PLATELET RESPONSE, 1945 THROUGH 1954

| | THROMBOPENIC PURPURA, CASES | | |
|---|---|---|---|
| | ACUTE | CHRONIC | TOTAL |
| Total | 26 | 52 | 78 |
| Splenectomy | 14 | 40 | 54 |
| Platelet response | | | |
| Immediate | 11 | 26 | 37 |
| Delayed | 2 | 4 | 6 |
| None | 1 | 7 | 8 |
| Incomplete data | — | 3 | 3 |

## SUMMARY AND CONCLUSIONS

Among 187 patients with purpura who were less than 15 years of age and who were seen at the Mayo Clinic in the period 1945 through 1954, the ratio of patients with thrombopenic purpura to those with nonthrombopenic purpura was 4 to 3. Most pa-

tients were in the younger age groups, that is, 6 years of age or less. The frequency with which infections preceded the onset of purpura was noteworthy.

The outlook for recovery with conservative treatment is good both in nonthrombopenic and in acute thrombopenic purpura. Our experience with steroid hormone therapy in the control of bleeding has been disappointing.

Splenectomy was performed on fifty-four of seventy-eight patients who had idiopathic thrombocytopenic purpura, with two deaths. The risk of intracranial bleeding and of the continuance of purpura into adult life or into the menstrual age in girls should be considered in the determination of the treatment to be used.

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# PARINAUD'S OCULOGLANDULAR SYNDROME

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THE syndrome of a granulomatous conjunctivitis with associated preauricular or submaxillary adenopathy was first described by Parinaud in 1889.[1] Since then numerous reports of this interesting condition have appeared in the ophthalmological literature. It is the purpose of this paper to draw general attention to this syndrome and to emphasize its importance in the differential diagnosis of a preauricular tumor.

## CASE REPORT

E. L., a 7-year-old boy, had been entirely well until about ten days before admission, when he started to develop a swelling in front of his left ear. This swelling increased in size and was not painful or tender to touch. At about the same time, a minor squint was noted in his left eye. There had been neither fever nor any other symptoms, and his appetite had remained good. There had been no known exposure to any infectious diseases. There was no recollection of a cat scratch although the boy was frequently in contact with cats.

On physical examination the child was well developed, well nourished, and afebrile. The color was good and there were no ecchymosis or petechiae. The heart was normal, the chest was clear and the blood pressure was 105/70. The abdomen was soft without tenderness or masses. There was no adenopathy except for an olive-sized tumor in the left preauricular area which was firm, movable, and not tender. The overlying skin was not reddened. Central nervous system examination was entirely negative except for a left internal strabismus.

On admission the white blood count was 7,200 with 52 per cent neutrophils, 9 per cent bands, 39 per cent lymphocytes; the hematocrit was 38 mm., and the hemoglobin was 77 per cent. The urine was negative. The sedimentation rate was 9; the heterophil agglutination was negative as were agglutinations against typhoid, paratyphoid, brucellosis, and tularemia. A Hinton test was negative. An x-ray series including the skull, all the long bones, as well as a chest film were all within normal limits.

The patient was asymptomatic throughout his hospital stay except for a nightly rectal temperature elevation up to 100.5° F. On the second hospital day it was suggested by a surgical consultant that the preauricular mass be removed in order to establish a diagnosis. Later that morning the patient was seen by an ophthalmologist for an opinion on the left strabismus and its possible relationship to this tumor. According to this consultant, the appearance of the eye was due to edema of the upper lid and not due to strabismus. Upon everting the upper lid he demonstrated a peculiar type of conjunctivitis. Numerous irregular, 1 to 5 mm., reddish-brown nodules were present on the upper palpebral conjunctiva. It was apparent then that the mass in the left preauricular area was secondary to this conjunctivitis, and that surgical exploration would not be needed.

Smears and cultures of this follicular conjunctivitis showed only *Staphylo-*

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*coccus albus* and alpha hemolytic streptococcus. A biopsy of the upper lid disclosed no specific etiology. On microscopic examination, the biopsy showed a partially eroded stratified epithelium beneath which there was fibrocollagenous tissue. The surface of this tissue was extensively infiltrated by lymphocytes, plasma cells, scattered macrophages, and eosinophils. In one of the sections, several multinucleated foreign body type giant cells were seen. No organisms could be found on routine or special stains.

After the cultures of the eye were taken, the patient was started on

Fig. 1.—E. L. with a left preauricular tumor as he presented himself on admission to the Burbank Hospital.

Fig. 2.—The everted upper lid with the characteristic nodules of Parinaud's conjunctivitis.

Aehromycin by mouth and sulfathiazole ophthalmic ointment locally. He was discharged on this treatment on the seventh hospital day. By that time, a noticeable diminution in the preauricular adenitis had occurred. When seen one week later he had been afebrile and the adenitis and conjunctivitis had improved considerably. Two weeks after discharge, the conjunctivitis and adenitis had completely disappeared and treatment was terminated.

## DISCUSSION

The boy described above presented himself with a painless preauricular tumor. Complete physical examination was otherwise negative except for what was initially interpreted as a minor squint. Complete blood studies were normal; a negative heterophil refuted a diagnosis of infectious mononucleosis; and a normal sedimentation rate seemed somewhat to favor a noninfectious nature of the tumor. The eyes on superficial examination appeared normal except for the "minor squint" in the left eye. If the upper lid had not been everted, the follicular conjunctivitis, causing the preauricular adenitis, might have been missed entirely since only the tarsal conjunctiva was affected. The knowledge of the ophthalmological consultant, who recognized this as Parinaud's oculoglandular syndrome and thereby ruled out lymphoma or mixed parotid tumor, saved the boy from an unnecessary exploration with possible damage to the facial nerve.

Awareness of the fact that the upper lid drains into the preauricular node is of utmost importance. Therefore, in unexplained preauricular adenitis the upper lid should be everted

lest Parinaud's oculoglandular syndrome be overlooked.

To date, only ophthalmologists have contributed to the literature on this syndrome and their contributions with few exceptions[2-4] have appeared in ophthalmological journals. The first account appearing in the American literature was by Verhoeff and Derby[5] in the *Archives of Ophthalmology* in 1904.

The fungus leptothrix was first recognized by Verhoeff[6] in sections of material taken from the diseased conjunctiva. Since then it has been found that it is the most common cause of Parinaud's conjunctivitis. In 1918 Wherry and Ray[3] isolated the leptothrix from material of a preauricular gland for the first time and in 1940 Verhoeff[4] described an improved method of staining this organism.

Etiological agents other than leptothrix may infrequently produce this clinical picture. They are, according to Henry[2]: tuberculosis, oculoglandular tularemia, syphilis, lymphogranuloma venereum, sporothricosis, glanders, Bacillus pseudotuberculosis-rodentium, soft chancre, and vaccinia. In addition, *B. proteus*,[7] yeastlike organisms,[8] and cat-scratch disease[9] may be responsible for the picture of Parinaud's conjunctivitis. Therefore in order to establish an etiological diagnosis, the following laboratory studies should be undertaken: (1) a biopsy of the necrotic area with examination of the sections carefully stained by Verhoeff's method[4]; (2) smear and cultures of the lesion, including a culture made according to the technique of Verhoeff and King[10]; (3) a tuberculin test—if positive, a guinea pig inoculation with ground-up pathological conjunctival material; (4) a serology; (5) an agglutination test for tularemia, (6) a Frei test, and (7) an intradermal test with cat-scratch antigen.

Verhoeff and King[10] found the leptothrix in biopsy sections from forty-four out of forty-five patients examined. However, other authors found laboratory confirmation very difficult. Henry[2] described eight cases of leptothrix conjunctivitis, but was able to confirm the diagnosis by laboratory means in only three patients.

Parinaud's oculoglandular syndrome is a disease of the conjunctiva associated with preauricular or submaxillary lymphadenopathy occurring chiefly in children and young adults. It is usually unilateral, involves the tarsal conjunctiva, and consists of gray or yellowish necrotic areas beneath the epithelium. These areas measure from ½ to 4 mm. in diameter and may be multiple or single. They are usually associated with the formation of nodules and follicles. The conjunctiva is edematous; secretions are scanty or absent. History of close contact with cats is common. The constitutional symptoms are slight and consist of a low-grade fever and painless enlargement of the regional lymph glands. A mild eosinophilia[2] is frequently present. The course is usually benign with spontaneous healing in one to three months,[2] leaving no residual damage. Complications of this condition are uncommon. Occasionally suppuration of the preauricular node[5, 11, 12] and, more rarely, hemorrhage into the conjunctival nodule with ecchymosis of the conjunctiva[12] may develop.

Treatment in the preantibiotic era was by excision of the gray areas and nodules. Henry[2] felt that the course of this self-limited disease was considerably shortened by the use of sul-

fonamides. The boy discussed above responded so promptly to Achromycin by mouth and sulfathiazole ophthalmic ointment locally that the conjunctivitis and the secondary adenitis had completely subsided after three weeks of treatment.

## SUMMARY

A case of Parinaud's oculoglandular syndrome is described in a 7-year-old boy, who presented himself as a differential diagnostic problem of a preauricular tumor. The syndrome consists of a granulomatous conjunctivitis with associated regional lymphadenopathy.

If an unexplained preauricular mass is found, the upper lid should be everted and examined for the conjunctivitis of Parinaud.

Treatment with Achromycin by mouth and sulfathiazole ophthalmic ointment locally shortens the self-limited course of this syndrome.

Studies necessary to demonstrate an etiological agent are reviewed and it is emphasized that laboratory confirmation is difficult even under the best circumstances.

I wish to acknowledge the help of Dr. Samuel C. Golden who, as the ophthalmological consultant, suggested the correct diagnosis, and of Drs. Judd H., and Seda Sparling of the pathology department. I am also indebted to Dr. Winston G. Stewart for the photographs.

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# SUPERIOR VENA CAVAL OBSTRUCTION IN CHILDHOOD

## Report of a Case Secondary to Histoplasmosis

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THE syndrome of superior vena caval obstruction results from partial or complete obstruction of the venous flow in the portion of body which normally has its venous return through the superior vena cava. Delayed circulation time, an established collateral circulation, and the associated symptoms common to the primary disease process account for the presenting clinical picture. Any condition which interferes with blood flow through the superior vena cava, without a corresponding interference in the inferior vena cava, may produce the syndrome.

Ochsner and Dixon[1] state that "obstructions to the superior vena cava whether partial or complete are rare clinical and pathological entities." According to Forster,[2] obstruction of the superior vena cava is not uncommon. Mc Intire and Sykes,[3] in an extensive and complete review of the literature in 1949, recorded 522 previously reported cases and two of their own. The opinion of these authors is that the syndrome is not rare in view of the frequency of space-occupying lesions of the superior mediastinum, the anatomical relationships of the superior vena cava, the easy compressibility of the vessel, and the large number of cases reported in the literature of many years.

Primary thoracic tumors, aneurysms, and chronic fibrous mediastinitis are responsible for the obstruction in 75 to 80 per cent of the cases. In the twenty-seven cases reported by Hussey and associates,[4] in which the cause was verified, all obstructions were due either to aneurysm or a malignant neoplasm. Simple thrombosis of the superior vena cava is very rare. Other less frequent causes of obstruction are propagating thrombi from the periphery, localized phlebitis with thrombus formation, actinomycosis, and obliteration of the pericardium.

Chronic fibrous mediastinitis of both specific and so-called nonspecific or idiopathic types has been described; it is the cause of approximately 15 per cent of all cases of superior vena caval obstruction. Traction or compression by scar tissue is the cause of obstruction in such instances. In the specific varieties, both tuberculosis and syphilis have frequently been implicated. Other antecedent etiological factors such as upper respiratory infection, influenza, bronchopneumonia, tularemia, trauma, rheumatic fever, and the tendency to form excessive amounts of cicatricial tissue (keloid) have been

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observed in occasional cases. Because of the present widespread usage and effectiveness of chemotherapy and antibiotic therapy in many acute respiratory infections, it is reasonable to anticipate a decrease in the incidence of mediastinitis secondary to such types of infection.

In the comprehensive review of Mc Intire and Sykes, superior vena caval obstruction was more common in males than females in the ratio of 4:1. The highest age of incidence is between 30 and 60 years, probably corresponding to the age of incidence of the common etiological factors as neoplasms and late syphilis, including aortic aneurysm. In the cases reviewed by these authors, one patient less than 10 years of age, with superior vena caval obstruction, had been reported in the period from 1904 to 1946. It is possible that certain cases of superior vena caval obstruction may have been reported as cases of the primary pathology, such as aortic aneurysm and mediastinal lymphoma.

A report of a case of superior vena caval obstruction from fibrous mediastinitis due to histoplasmosis has not been noted in the literature on this subject. Also, obstruction of the superior vena cava from any cause in childhood is most rare. This report of a case in a female child 7 years of age, due to extensive scarring from pulmonary histoplasmosis with apparent complete recovery subsequent to thoracotomy, is unusual in all respects.

## CASE REPORT

J. M., female, aged 7 years, was first seen at Carle Memorial Hospital on Sept. 3, 1954. The family history was irrelevant. The child lived in a rural community of southern Illinois. Birth and developmental histories were normal.

In March, 1951, she had rubeola with subsequent "virus pneumonia." From March, 1951, until October, 1951, she was recurrently ill with colds and cough. Roentgenographic studies of the chest during the same period were reportedly negative. Since 1951 she had been subject to recurrent upper respiratory infections, sore throats and bronchitis, and had suffered some weight loss.

On Aug. 30, 1954, she developed right chest pain, referred to the right shoulder and scapular areas, and she vomited. Because anterior poliomyelitis was suspected by the family physician, she was referred to Carle Memorial Hospital on Sept. 3, 1954.

On physical examination the patient appeared ill and was coughing. Weight was 64 pounds, temperature 97°, and blood pressure 100/60. The tonsils were slightly enlarged, the pharynx was injected and the anterior cervical nodes were palpable and tender bilaterally. An inconstant, soft systolic murmur was noted to the left of the sternum. Examination was otherwise noninformative. Urinalysis was negative. A hemogram disclosed hemoglobin 10.6 grams, erythrocytes 3,700,000, leukocytes 6,500 with 72 per cent neutrophils, 25 per cent lymphocytes, 2 per cent monocytes, and 1 per cent basophils. The erythrocyte sedimentation rate (Westergren) was 47 mm. in 45 minutes. Agglutinations for typhoid, paratyphoid, brucella abortus, brucella melitensis, and $OX_{19}$ were negative. The electrocardiogram was normal. Roentgenograms of the chest disclosed pleural thickening at the right apex and along the right upper mediastinum. There was right hilar and peritracheal lymphadenopathy. Small scattered areas of fibrosis and calcification were present in both lung fields, with rather marked fibrosis or infiltration in the upper two-thirds of the right lung (Fig. 1). A skin test with old tuberculin 1:1,000

was negative, and the skin test with histoplasmin was strongly positive. Serological studies performed at the U. S. Public Health Service Laboratory, University of Kansas Medical Center, Kansas City, Kansas, on blood serum drawn Sept. 9, 1954, were positive 1:64 (histoplasma yeast phase antigen complement fixation test).

The patient was hospitalized from Sept. 3 until Sept. 19, 1954. On September 7, 8, and 9 the temperature varied from 103° to 104° F. Roentgenograms of the chest showed marked infiltration of the right upper

Fig. 1.—Pleural thickening at the right apex and right upper mediastinum is demonstrated. There are enlargement of the right hilar and peritracheal lymph nodes and marked fibrosis or infiltration in the upper two-thirds of the right lung.

lung field. During this period there was nasopharyngitis with evidence of adenotonsillitis and she complained of discomfort in the right chest, chiefly on inspiration. Treatment with chlortetracycline, penicillin, and streptomycin caused no perceptible improvement. On chloramphenicol the temperature declined and by September 14 she was much improved and the temperature low grade. Both the cough and complaint of right chest pain diminished. Roentgen studies showed moderate clearing of the parenchymal infiltration in the right upper lobe. The sedimentation rate on September 17 was 72 mm. but the child appeared markedly improved. Repeated complete blood counts were similar to the hemogram at admission.

The patient was dismissed on absolute bed rest, iron, and vitamins, and thereafter was seen periodically as an outpatient. Blood cultures for histoplasma capsulatum drawn in October, 1954, and again in December, 1954, were negative after being held two and three months, respectively. The serology on blood serum obtained October 6 remained strongly positive. She gained in weight and generally did well, although several weeks subsequent to dismissal she had hyperpyrexia for several days. The sedimentation rate declined gradually but was never in the normal range. On Dec. 20, 1954, a roentgenogram of the chest showed some increase in infiltration of the right upper lobe with enlargement of the peritracheal lymph nodes on the right.

About Dec. 25, 1954, the child's parents observed that the patient's face appeared full, although she was feeling well, gaining weight, and without complaint. A chest roentgenogram on Jan. 24, 1955, showed consolidation of the right upper lobe. This was regarded as fibrosis and atelectasis resulting from the fibrotic process in the right chest. The sedimentation rate on January 24 was 25 mm. Though a slight cough persisted, she appeared generally well.

On Feb. 17, 1955, she was seen because of swelling in the face and upper trunk; the parents had noted the swelling for several weeks prior to this examination. The face was full and puffy, and dyspnea with moderate cyanosis of the face and lips was apparent. The neck, arms and shoulders appeared large and edematous, and veins over the lower right chest were prominent. Dyspnea increased when she reclined. Temperature was 98° F., pulse 104, and blood pressure 110/50. Roentgenograms of the chest showed extensive infiltration and par-

tial atelectasis of the right upper lobe with some clearing of the infiltrations in the right middle and lower lobes (Fig. 2). Studies of venous pressure were not attempted. A diagnosis of superior vena caval obstruction from mediastinal fibrosis secondary to pulmonary histoplasmosis was made, and she was referred to Dr. Amos Christie, Nashville, Tennessee, for consultation. He concurred in this opinion and on March 10 a thoracotomy was performed by Dr. Rollin A. Daniel, Jr., at Vanderbilt University Hospital.

At surgery a large mass of nodular dense fibrous tissue which filled the superior mediastinum and extended downward along the right border of the pericardial sac to encompass the hilar structures of the right lung was observed. The right upper lobe appeared moderately contracted and scarred but did contain air. The fibrotic scar completely surrounded the superior vena cava for a distance of 2 cm. in its mid-portion. The scar was freed until the wall of the vena cava was exposed for over two-thirds of its circumference. The pericardial sac was widely opened during this dissection, and a portion of the pericardium involved in the scar was excised. The wall of the superior vena cava was leathery and scarred but the lumen of the vessel was re-established, although marked narrowing persisted at the site of greatest scarring. Sections of scar removed at surgery revealed fibrous connective tissue with some scattered inflammatory cells, and there was no histologic evidence of neoplastic tissue. Recovery from surgery was uneventful, and edema of the face, neck, chest, and upper arms gradually subsided. Histoplasma capsulatum could not be demonstrated in sections of the scar tissue.

Her postoperative course was uneventful, and the puffiness of the face, neck, and upper trunk rapidly diminished. The previously prominent collateral circulation became less prominent. When examined at Carle Clinic on April 25, 1955, the patient weighed 77 pounds and appeared in good health. Because of a prominent keloid at the site of the operative wound, superficial x-ray therapy was given to the keloid, with moderate regression of the lesion. Roentgenograms of the chest on April 25 showed marked resolution of the process in

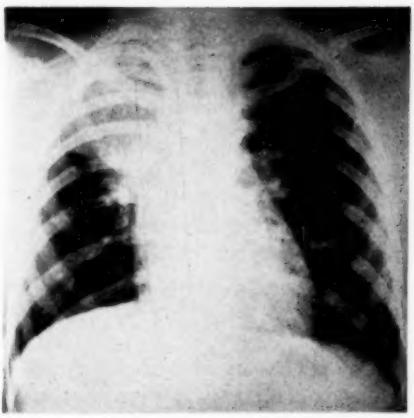

Fig. 2.—Infiltration and partial atelectasis of the right upper lobe with clearing of the infiltration in the right middle and lower lobes are noted.

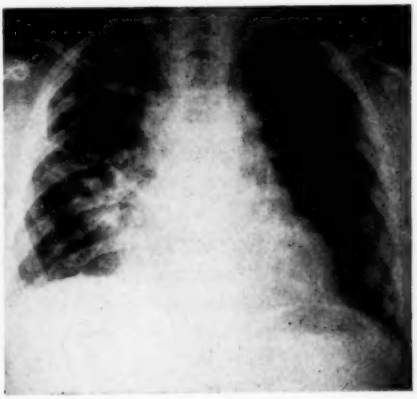

Fig. 3.—There is marked clearing of the right upper lobe atelectasis and infiltration, with moderate spread of the process in the right lower lung.

the right upper lung. Accentuation of markings persisted with small scattered areas of infiltration and some minute calcification in both lung fields. The sedimentation rate on the same day was 14 mm. (Westergren).

On June 9 weight was 84 pounds, but she complained of pain about the right shoulder and neck. Temperature was 102° F. Physical findings were negative except for mild pharyngitis. Roentgenograms of the chest demonstrated clearing of the right upper lobe lesion but increase in the infiltrations in the lower lung (Fig. 3). She was treated with antibiotics and remained febrile for one week.

Since July, 1955, the child has remained entirely well, free of complaint, and entered school in the fall of the year. Two roentgenograms of the chest, one in August and the other in November, 1955, were essentially negative.

## DISCUSSION

Complete obstruction of the superior vena cava, or nearly so, is usually diagnosed from the history and physical findings. Sudden onset is characterized by edema, dyspnea, and cyanosis of the areas drained by the superior vena cava. The edema results from increase in venous pressure and is aggravated when the patient is recumbent, because in this position the venous pressure is higher. The cyanosis is due to distention of the capillaries and the tremendous increase in volume of blood in the veins emptying into the superior vena cava. These factors cause the many subcutaneous venules noted especially in the region of the sternum and lower rib margins. When the superior vena cava is gradually obstructed, a collateral circulation develops more or less concurrently, thereby modifying the clinical picture and the pattern of collateral veins varies according to the point of obstruction of the superior vena cava.[5] Dyspnea, cyanosis, and edema are less prominent with gradual obstruction.

A comparison of measurements of venous pressure in the antecubital and femoral veins will substantiate the diagnosis of the superior vena caval syndrome for in any case pressure will be significantly higher in the antecubital vein. Such studies were not undertaken in this patient since veins were not easily accessible.

Superior vena caval obstruction is not always incompatible with relative good health. Rose[6] reported obstruction of the superior vena cava of twenty-five years' duration in which thrombophlebitis secondary to carbuncles of the chest was the suspected cause. McCord and associates[7] reported a patient who died fifty years after the development of evidence of collateral circulation subsequent to a febrile illness in childhood, the superior vena cava having been completely obstructed by a fibrocalcific mass.

The diagnosis of histoplasmosis in the reported case is presumptive in that cultures and pathological specimens failed to demonstrate histoplasma capsulatum. Nevertheless, the strongly positive skin test, the positive titer in relatively high dilutions on two occasions, the chronic febrile illness, and chronic pneumonia warrant a diagnosis of histoplasmosis as the cause for the obstruction of the superior vena cava in this case.

Superior vena caval obstruction from any cause is apparently very rare in the younger age groups. While chronic fibrous mediastinitis causes approximately 15 per cent of

all cases of this disease, reported cases in which the primary pathology was histoplasmosis have not been noted in the literature. Since histoplasmosis is not uncommon, particularly in the Mississippi Valley area, it is possible that some previously reported cases of so-called idiopathic fibrous mediastinitis may have been of histoplasmosis origin.

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*The Fallynge Evyll Called in the Greke Tongue Epilepsia*

Not only other ages but also lytle chyldren are oftentimes afflycted with this gryevouse syckenes, some tyme by nature receyved of the parents and then it is impossible or difficile to cure, sometime by evil and unholsome diet whereby there is engendred many colde and moist humors in the brayne whereupon this infirmity procedeth, which if it be in one that is young and tender it is very hard to be removed, but in them that are somewhat strong as of seven yeres and upwarde, it is more easye.

I fynde that manye thyngs have a natural vertue against ye falling evill, not of any qualitye elementall but by a singuler propertye or rather an influence of heaven whiche almyghtye God hathe geven into thynges here in earth, as be these and other, saphires, smaragdes, redde coral, piony, mystletow of the oke taken in the moneth of March and moone decreasynge, savein, dylle, and the stone that is founde in the bellye of a yonge swallow being the first brood of the dame. These or one of them hanged about the necke of the child saveth and preserveth it from the sayd sickness.

—From Thomas Phaer, 1544.

# DUPLICATION OF THE TERMINAL ILEUM

## Report of a Case

Howard Boyd, M.D., and Merrill B. Rubinow, M.D.
Manchester, Conn.

Gross[1] defines duplications of the alimentary tract as spherical or elongated structures composed of smooth muscle lined with mucous membrane. They are intimately attached to some portion of the alimentary tract and at times communicate with the parent viscus. We feel justified in presenting this case because, although it is uncommon, the condition is amenable to surgery and early diagnosis is essential to prevent high mortality.

In a comprehensive review of the literature LoPresti and co-workers[2] recorded 150 cases of intestinal duplication up to 1950. Of this number 115, or 77 per cent, were in the region of the small intestine. Gross and associates[3] added twenty-seven more cases in 1952 and these demonstrated the same regional distribution. Potter[4] described the only case of duplication in her series of autopsies. Its dimensions were 6 by 8 cm. and 10 cm. from the ileocecal valve. There was a mucus-filled cyst whose outer muscular layer was fused with that of the ileum. The ileum was completely collapsed by pressure from the enlarging duplication. Fox and Fowler[5] discussed duplication and reported a case. They presented the most common symptoms as vomiting, diarrhea, melena, and colic. The most characteristic physical finding was a movable mass. Flat film of the abdomen and barium enema might suggest the diagnosis but it was rarely made before operation.

From the Manchester Memorial Hospital.

### CASE REPORT

P. B., a 3-day-old female infant, was the product of a normal gestation and delivery. On her third day she refused feedings, vomited once, and had a temperature of 101° F. Up to this time she had taken her formula well and had passed meconium. Physical examination failed to offer a satisfactory explanation for the infant's illness. Because sepsis was suspected, blood was taken for culture. There was no growth. White blood count was 15,750 of which 67 per cent were neutrophils, 26 per cent lymphocytes, and 7 per cent monocytes. The red blood count was 4,470,000 with a hemoglobin of 13.3 grams. The blood was typed for transfusion. Penicillin and dihydrostreptomycin were given. The next day the baby had a distended abdomen and a movable mass the size of an English walnut was felt in the right lower quadrant. This mass could be felt between the hand on the abdomen and a finger in the rectum. On the examining glove there was bloody mucus. The nurses reported that the baby had just passed a peculiar, light-colored, tough stool followed by bloody mucus. The plain film of the abdomen showed gas-filled loops of small bowel, chiefly on the left side, and the interpretation was that of intestinal obstruction associated with a right-sided mass. The barium enema was reported as follows: "After the injection of an

enema under fluoroscopic guidance the barium is seen to flow readily to the cecum without obstruction and enter the terminal ileum. There is no evidence of intussusception in the colon or terminal ileum. The barium-filled appendix can be seen extending from the cecal tip. There is no malrotation of the colon. There are several gas-filled and somewhat dilated loops of intestine in the upper abdomen and left side. There is a normal terminal ileum back for a distance of 6 to 8 cm. but at this point there is an abnormal segment of small intestine which is not understood and partially filled with barium and there are proximal to this point dilated small bowel loops. After evacuation the colon is well emptied. Conclusions: There is no evidence of intussusception in the colon. Dilated small intestinal loops proximal to a point about 6 to 8 cm. from the ileocecal valve. The possibility of some sort of a duplication of the small intestine at this point is suggested."

Fig. 1.—Barium enema showing narrowed ileum.

The preoperative diagnosis was small intestinal obstruction probably due to Meckel's diverticulum. After a Levin tube was placed in the stomach and a cannula introduced into the great saphenous vein, open-drop ether anesthesia was instituted. The abdomen was entered through a right lower quadrant transverse incision and found to contain about 200 c.c. of clear straw-colored fluid. The presenting mass in the right lower quadrant was delivered and found to be a cystic structure approximately 3 cm. in diameter protruding from the mesenteric border of the terminal ileum into the leaves of the mesentery about 12.5 cm. from the ileocecal valve. The small bowel up to this point was dilated and distal to this point collapsed, an indication of essentially complete small bowel obstruction. The cystic structure could not be removed because of its common wall and common blood supply with the ileum. It was felt necessary to resect the bowel and in order to protect the integrity of the anastomosis in the face of the marked distention of the proximal bowel loop, a side-to-side union was performed. The mesenteric defect was closed and

Fig. 2.—Drawing of lesion found at operation.

the abdominal wall closed in layers. Numbers 0000 and 000 silk suture material was used for the operative procedure. Blood transfusions and intravenous fluids were given throughout the operation.

Pathological examination of the specimen revealed a sleeve of intestine 4.5 cm. in length, 1.5 cm. in diameter at one end, and 0.7 cm. in diameter at the other. A sac 2 cm. in diameter in the collapsed state was attached to the mid-portion of the intestine. The wall of the sac was 0.3 cm. thick and its inner lining furrowed and velvety. There was no opening between the sac and the lumen of the intestine. The lumen of the bowel was essentially collapsed by the pressure of the cystic structure. Microscopically the wall of the duplication consisted of mucous membrane with epithelium and underlying fibrous stroma infiltrated with lymphocytes. Outside this was a layer of muscularis mucosae and then loose, edematous, hemorrhagic fibrous tissue. Beyond this layer was a muscular wall and then peritoneum with a fibrinohemorrhagic exudate on the mesenteric side. On the antimesenteric aspect of the sac the musculature was shared in common with the intestine and beyond this muscular layer was a small intestinal pattern which was normal histologically. The pathological diagnosis was duplication of the small intestine.

Postoperatively the course was essentially benign. Gastric suction was continued for forty-eight hours and on the second postoperative day the infant's bowels began to move and the distention lessened. The infant was gradually placed on an adequate diet and discharged from the hospital on the twelfth postoperative day. Following discharge she had frequent difficulties and was hospitalized on four occasions. In November, 1951, at the age of 9 months she was hospitalized for six days with bronchopneumonia. In November, 1952, one year later, the child entered the hospital in poor condition after having diarrhea, vomiting, and a convulsion at home. She responded to therapy and on this admission it was found that she had a congenital anomaly of the kidneys, consisting of a duplication of the collecting system of both kidneys. In January, 1955, when almost 4 years of age, she entered the hospital for rectal bleeding and was found to have a hemoglobin of 8.8 grams. After transfusions the hemoglobin rose to 12.8 grams and the child was discharged without further investigation because of the family's request. Her most recent admission was a few months later at the age of 4, when the blind loop of ileum resulting from the previous anastomosis was resected and the ileum reconstructed with an end-to-end anastomosis. The child was discharged, well, after this operative procedure and has had no difficulties since that time.

## DISCUSSION

The symptoms and clinical picture of intestinal duplication depend completely upon the anatomy and physiopathology of the condition. The most important anatomical consideration is the duplication's having a common blood supply and muscular wall with the associated intestine.[6] Enlargement of the duplication may produce pain, obstruction, interference with blood supply, ulceration, rupture, melena, intussusception, or fistula.[5, 7] Differential diagnosis is extensive and the correct preoperative diagnosis is seldom made. Meckel's diverticulum, intussusception, and mesenteric cyst are the most frequently encountered conditions which must be differentiated, according to Barrett.[8] Fisher[9] pointed out that the surgical treatment of duplications has become well defined since the antibiotics have mitigated the harsh mortality rate of bowel resection in the very young. As Fecher and associates[10] stressed, the treatment of choice is intestinal resec-

tion and anastomosis, preferably of the end-to-end variety. Hardaway and others[11] presented such a case in which there was successful operation on the fifth day of life. Unfortunately this end-to-end anastomosis cannot always be performed and it is hazardous in the face of obstruction with a dilated proximal bowel loop. As Fisher[12] demonstrated, the side-to-side anastomosis is much safer and the possibility of subsequent "blind loop" complication is a small price for this extra safety.

## SUMMARY

A case of duplication of the terminal ileum in the newborn infant has been presented. This patient developed the classical picture with a mass, intestinal obstruction, and bleeding. A successful small bowel resection was performed on the fourth day of life. The child subsequently developed a "blind loop" of proximal ileum due to the side-to-side anastomosis and four years later this was successfully resected and an end-to-end anastomosis performed.

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There is, moreover, a certain tact necessary for successfully investigating the diseases of children. If, when summoned to a sick child, you enter the room abruptly, and going at once to your patient, you begin to look closely at it, while at the same time you question the mother or nurse about its ailments in your ordinary pitch of voice, the child, to whom you are a perfect stranger, will be frightened, and will begin to cry; its pulse and respiration will be hurried, its face will grow flushed, and you will thus have lost the opportunity of acquainting yourself with its real condition in many respects. Besides this, the child's alarm once excited, will not subside so long as you are present; if you want to see its tongue, or auscultate its chest, its terrors will be renewed, and it will scream violently: you will leave the room little wiser than you entered it, and, very likely, fully convinced that it is impossible to make out children's diseases.

CHARLES WEST: LECTURES ON CHILDREN

# Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

## CLINICAL HISTORY

A WHITE male infant was admitted to The Children's Medical Center for the first time at 21 months of age, with a history of a four-month illness.

The past and family histories were noncontributory.

The patient was apparently a well, healthy, active boy until the age of 17 months, at which time he suddenly developed a chill, became pale and cyanotic, and the temperature was found to be 105.8° F. He had a generalized convulsion and was hospitalized. Between then and hospitalization here, he had three hospital admissions. Initial blood culture and almost every subsequent one yielded *Escherichia coli* (subsequently typed as Group 6). Attempts to eradicate this were intensive. He was given six separate, "adequate" courses of Chloromycetin, sulfadiazine, Aehromycin, neomycin, streptomycin, and polymyxin. He was also given 200 ml. of immune serum from his mother after she had been inoculated with the *Esch. coli*. The neomycin caused albuminuria, but otherwise no obvious deleterious effect was noted. *Esch. coli* continued to grow. Frequent physical examinations were unrevealing initially, except for splenomegally. No heart murmur was ever heard according to the family and the protocol sent here with the patient.

Other laboratory tests, including x-rays of the chest, skull, long bones, intravenous pyelogram, and biopsy of lymph node and bone marrow, were negative. A surgical exploration carried out in another city, prior to admission here, was complete but unrevealing. The liver (recently enlarged) especially was investigated for the presence of abscess.

Because of the patient's continued fever, failure to respond to the administered medication, and generally poor condition, he was given cortisone (200 mg.) and was referred here two days later.

On physical examination the temperature was 98° F., the pulse 100, the respirations 24, and the blood pressure 106/64. The weight was 22 pounds. The patient appeared pale, and chronically ill, but was in no particular discomfort. There was no significant lymphadenopathy. The lungs were clear. There was no cardiac enlargement. A rumbling low-pitched murmur that was felt to be diastolic

(later proved to be by phonocardiogram) was heard in the third to fourth left intercostal space. It was well localized. The pulmonic second sound was greater than the aortic second sound. The liver was down approximately 4 cm.; the spleen, 5 cm.

Urinalysis revealed 1 plus albuminuria, a specific gravity of 1.011 on a random specimen, and the sediment contained 3 or 4 white blood cells. The blood hemoglobin was 11.1 grams per cent, the white blood cell count 8,400, with 75 per cent polymorphonuclear leukocytes. The nonprotein nitrogen was 55 mg. per cent. The sedimentation rate was 3 mm. per hour, corrected. The tuberculin test was negative. Febrile agglutinations were negative. An electrocardiogram was interpreted as consistent with myocardial damage. A blood culture again yielded *Esch. coli*, Group 6. The patient's serum was found to have a titer against both "O" and "H" antigens: 1:80 in the "H," at least 1:360 in the "O" against the isolated organism. The mother had no demonstrable titer against *Esch. coli*. X-ray studies were noncontributory.

The temperature ranged from 104° to 105° F. He was started on sulfadiazine and Chloromycetin in high dosage, then polymyxin and streptomycin were added. Blood cultures continued to be positive. Frequent transfusions were necessary because of "refractory" anemia. Twenty-three days before death, the patient became irrational and tetanic. The plasma pH was 7.52. The calcium was 7.0 mg. per cent, the phosphorus was 3.2, the $CO_2$ 40.5, the sodium 127, the potassium 5.1, and the chloride 75 meq. per liter. Over the next few days it was discovered by study of twenty-four-hour urine specimens that he was losing large amounts of sodium and potassium. He was given sodium (60 to 80 meq.) and potassium (20 to 40 meq.) every day from then on to keep him in electrolyte balance. The nonprotein nitrogen dropped to "less than 12" about twenty days before death, but rose to 52 mg. per cent about the time of death. His condition gradually deteriorated. He developed thrombocytopenia, petechiae, and buttock abscesses from intramuscular antibiotics. The heart murmur persisted and, if anything, became louder. Twelve days before death sensitivity tests were repeated and again showed relative insensitivity to streptomycin, Furadantin, Chloromycetin, Terramycin, and Achromycin, and complete resistance to penicillin, bacitracin, and Aureomycin. The patient was therefore put on intravenous Terramycin and cortisone (200 mg. per day) eleven days before death and concurrently his blood culture became negative. However, from this point on, yeast was cultured from the pharynx, urine, and stool. The patient continued a slow but now afebrile, rapidly failing course, became somewhat icteric and, in spite of a well-balanced intravenous and gavage feeding, an experimental fungicidal drug, antibiotics, and cortisone, died quietly, remaining quite responsive up to the time of death, thirty-two days after his last hospital entry.

## DISCUSSION

DR. BENEDICT F. MASSELL.*—It is apparent that we are dealing with a

*Dr. Benedict F. Massell is Assistant Clinical Professor of Pediatrics, Harvard Medical School, and Research Director, House of the Good Samaritan (Children's Medical Center).

child who at the age of 17 months developed an *Esch. coli* septicemia, which persisted in spite of attempts at therapy with various antibiotics, who developed certain complications, some related to the underlying disease, some perhaps related to the various treatments given, and who finally died five months after the onset of this illness.

In discussing this case I shall consider the following problems: (1) *Esch. coli* septicemia; (2) the possibility that in this case septicemia was due to the presence of an *Esch. coli* bacterial endocarditis; (3) the nature of the associated cardiac lesion, assuming that an *Esch. coli* bacterial endocarditis was present; (4) the treatment of bacterial endocarditis, particularly *Esch. coli* bacterial endocarditis; and (5) the complications that developed in this case.

The colon bacillus, like other gram-negative enteric bacilli, contains a somatic antigen, the so-called "O" antigen, which is highly toxic. Yet the colon bacillus is a normal inhabitant of the intestinal tract in man and ordinarily is not pathogenic. However, under certain circumstances it may cause serious infection. Certain strains in particular are known to be pathogenic even when they are confined to the gastrointestinal tract. For example, those identified by serologic typing as 0-26, 0-55, 0-111, and 0-127 have been most frequently identified in severe and often fatal diarrhea in infants. It is not clear in this case whether the *Esch. coli* that was isolated in the blood was one of these strains that are known to be pathogenic, because the isolated strain is said to be a Group 6 or Type 6. The method of typing here apparently is not the same as that used in the classification to which I just referred. *Esch. coli*, even when not one of the known pathogenic strains, may cause localized infections sometimes in association with other organisms. Examples are appendicitis, peritonitis, cholecystitis, and pyelonephritis. *Esch. coli* septicemia is not a common disease, but neither is it rare. Thus, in a cursory review of the literature, I found reports of some 400 cases of *Esch. coli* septicemia. In most of these instances, however, *Esch. coli* septicemia could be traced to certain definite causes. Usually it was secondary either to operation or to instrumentation involving one of the following tracts: urinary, genital, gastrointestinal, or biliary. In a small number of cases the septicemia was secondary to localized infections, such as pyelonephritis, appendicitis, or cholecystitis. I presume that the physicians responsible for this patient prior to his transfer to the Children's Hospital considered such an infection and, therefore, explored the abdomen. Apparently, however, a portal of entry for the infection was not found by the surgeon.

I have just been informed that the child had the peculiar habit of carrying and chewing a whisk broom. It is conceivable that there were *Esch. coli* on the whisk broom and that they entered through the respiratory tract, or perhaps a sharp piece of the whisk broom got into the intestinal tract. Possibly there were no *Esch. coli* on the whisk broom, but that one of the sharp fibers penetrated the intestinal tract, allowing the organism, which was not normally pathogenic when confined to the intestinal tract, to gain entrance to the blood stream.

Whatever the source of the infection, it seems likely that this patient had an *Esch. coli* endocarditis. The following aspects of the patient's clinical course are quite consistent with that diagnosis: the abrupt onset with chill; the persistence of a septic type of fever, except when the patient was given cortisone; the presence of a heart murmur; the enlargement of the spleen; and, of course, the finding of the numerous positive blood cultures for *Esch. coli.* If the patient had shown embolic phenomena (which I understand he did not show) this would have been additional evidence for the diagnosis of bacterial endocarditis, but the absence of such signs does not rule out that diagnosis. The organism, *Esch. coli,* is capable of producing metastatic abscesses, and, therefore, even though no signs of emboli were detected, we should not be surprised if we learn that the autopsy revealed abscesses due to *Esch. coli* in the viscera. It should be pointed out that, compared to other bacteria, *Esch. coli* is a quite uncommon cause of bacterial endocarditis. Also, the incidence of bacterial endocarditis in infants and very young children is low, compared to its incidence in older children and especially in adults. Therefore, if my diagnosis is correct, it must be concluded that we are dealing with a rare disease.

Now we come to a very difficult aspect of this case, namely, the nature of the heart lesion. Frankly, I am not going to be able to give a definite answer on that point. Bacterial endocarditis usually occurs in individuals who have an underlying cardiac defect. Rarely, especially in the acute variety, endocarditis can develop in a heart that previously has been entirely normal. In children the possible kinds of underlying heart disease that have to be considered are: (1) congenital lesions of various types; (2) rheumatic heart disease, usually with mitral and aortic valve involvement, and rarely with tricuspid involvement; (3) endocardial sclerosis or so-called endocardial fibroelastosis. I think we can dismiss this last diagnosis for the following two reasons: first, the condition itself is quite uncommon; second, endocardial sclerosis with murmurs is especially uncommon, particularly pure diastolic murmurs. Furthermore, I know of no cases of bacterial endocarditis complicating subendocardial sclerosis that have ever been reported in the medical literature. You did have one, Dr. Craig?

DR. JOHN M. CRAIG.—Dr. Farber reported one in 1932,[1] and we included that case in our 1949 article.[2]

DR. MASSELL.—I still think it is a very rare combination and especially unlikely when only a diastolic murmur is described.

Rheumatic heart disease also seems unlikely for the following reasons: first, rheumatic heart disease in children under 3 years of age is very rare; second, there is no history of underlying rheumatic fever to have caused rheumatic heart disease; third, no murmurs were present before the present illness; finally, the murmur was low pitched and diastolic. Such a murmur can occur in rheumatic heart disease, but it is usually maximal at the cardiac apex and not along the left sternal border. Furthermore, when a diastolic murmur is present at the cardiac apex in rheumatic heart disease, there is almost invariably an accompanying significant systolic murmur. Mid-diastolic murmurs do not occur alone. Rare instances of mitral

stenosis occur in very young children, but then a presystolic rather than a mid-diastolic murmur is present. We should also consider the possibility that this murmur along the left sternal border was actually an aortic diastolic murmur. From its description it is not characteristic of aortic regurgitation.

Am I correct in believing that there was a rumbling mid-diastolic murmur, not an early diastolic murmur?

DR. WARREN G. GUNTHEROTH.—It was mid-to-late, without a presystolic crescendo.

DR. MASSELL.—I would hesitate to make a diagnosis of rheumatic heart disease on the basis of these findings.

DR. CHARLES A. JANEWAY.—You would hesitate to make it in a 21-month-old infant, would you not?

DR. MASSELL.—Yes.

Finally, could this child have had an underlying congenital heart lesion? That, of course, is a very good possibility, because bacterial endocarditis in young children frequently complicates congenital heart lesions of various sorts, such as interventricular septal defect, patent ductus arteriosus, coaretation of the aorta, tetralogy of Fallot, and bicuspid aortic valve. The only lesion that is but rarely complicated by bacterial endocarditis is an atrial septal defect even though this is one of the more common types of congenital lesions.

In considering the type of congenital lesion, we have to keep in mind the fact that cyanosis was mentioned. However, I have the impression that cyanosis was not an outstanding feature of this case and that, before the child became acutely ill, there had been no cyanosis. I am, therefore, inclined to dismiss all lesions that might cause a right-to-left shunt.

Regarding the possibility of other congenital lesions, the difficulty in this case is that the murmur which has been described is not like any of those that one would expect in the various defects being considered, so that it is hard to judge its significance here. A low-pitched murmur such as has been described does occur in atrial septal defect.

DR. GUNTHEROTH.—Actually this murmur was more presystolic than it was diastolic. Dr. Nadas could not describe it as rumbling. He described the accentuated apical first sound, which was preceded by a mid-diastolic murmur, with a presystolic crescendo as recorded by the phonocardiogram. The murmur was not heard after the first sound.

DR. MASSELL.—I, personally, am not helped much by the phonocardiogram except for timing of murmurs. I think the timing is important, and the pitch might be important. I am a little disturbed by the fact that Dr. Nadas thought the murmur was presystolic; it makes things more difficult for me. Against the presence of an atrial septal defect are the facts that, first, when a diastolic murmur is present, it is usually associated with a systolic murmur; second, that bacterial endocarditis is an uncommon complication of atrial septal defect. Therefore, I am going to discard that diagnosis, too.

The electrocardiogram tracings, I find, are not especially helpful. The Q-T interval was said to be prolonged: at least I presume it was so by the interpretation. Actually this interval

was within the normal limits of a series of 500 normal electrocardiograms in children that we studied. There were definite T-wave changes. These could have been due to myocardial disease. A patient with *Esch. coli* bacterial endocarditis could very well have a toxic myocarditis. But it does not help us to define the underlying valvular defect or congenital defect. Furthermore, these types of changes in the electrocardiogram could well be explained by the low potassium and calcium levels in the serum.

Therefore, I must conclude that the cardiac findings described in this case are not much help in making a diagnosis, and anything I say about diagnosis of the heart lesion will be highly speculative. I am forced to say that the patient either developed bacterial endocarditis, without having any underlying defect, or he had some congenital lesion that does not ordinarily produce an outstanding murmur. The lesion that stands out foremost in this regard is a bicuspid aortic valve, which is commonly a point of bacterial endocarditis. If I have to choose, I will choose the diagnosis of a congenital bicuspid valve.

At various times this patient was given a number of antibiotics. Before he was admitted to the Children's Hospital, he received Chloromycetin, sulfadiazine, Achromycin, neomycin, streptomycin, and polymyxin. At the Children's Hospital he received sulfadiazine plus Chloromycetin, and then later he received all four drugs: sulfadiazine, Chloromycetin, polymyxin, and streptomycin combined. None of these courses of therapy had any favorable effect; the clinical course grew steadily worse, and the blood cultures, except at the very end, continued to reveal *Esch. coli*. The poor result in this case, however, is not surprising, in view of the fact that in vitro studies showed that the organism was relatively insensitive to streptomycin, Furadantin, Chloromycetin, Terramycin, and Achromycin and that it was completely resistant to Aureomycin and penicillin.

In considering this patient's poor response, one of the questions that arises is this: was the *Esch. coli* that caused this child's illness resistant to all these antibiotics in the beginning, or did the organism develop resistance during the course of therapy? Since quantitative sensitivity data are not available for us to compare the findings at the beginning of the illness with those at the end, there is no way of answering the question. However, it should be pointed out that, although *Esch. coli* are sometimes found to be sensitive in vitro to some of the antibiotics that have been mentioned here, many strains are often found to be resistant even before their exposure to the antibiotics during therapy. Therefore, without further data, it would be unwarranted to conclude that the *Esch. coli* in this case had actually become resistant as a result of therapy. Nevertheless, the case illustrates some of the principles that I consider to be fundamental in obtaining a maximum incidence of cure in cases of bacterial endocarditis. First, unless the patient's clinical course is very rapidly worsening, it is better to withhold therapy for a few days than to give treatment before adequate laboratory studies have been completed. This comment does not apply to the child's management at the

Children's Hospital because the patient had been under treatment a long while before he was transferred here. Second, the laboratory studies should include a sufficient number of blood cultures so that the infecting organism can be obtained in at least three different cultures (to be sure that the organism obtained is not a contaminant). Third, quantitative in vitro tests should be done to determine the organism's sensitivity or resistance to various antibiotics. Fourth, the patient should then be treated with the antibiotic or a combination of the antibiotics to which the organism is most sensitive, and the amount used should be an amount that would be expected to give blood levels well above those required to inhibit the organism in vitro. Fifth, antibiotic therapy should be controlled by a measurement of the blood levels actually being attained. Finally, better results are usually obtained if one selects an antibiotic that is primarily bactericidal rather than one that is only bacteriostatic.

Before leaving the problem of therapy, I think a few remarks are in order regarding two other forms of therapy that were used in this case. One is the giving of the isolated, killed, infecting bacteria or antigen to immunize the mother and then the giving of her hyperimmune serum to the patient. The other is the administration of cortisone. Long before antibiotics were discovered, the first type of therapy had been tried many times, and always without success. These poor results are not surprising, since patients who have bacterial endocarditis usually have high antibody titers in their own plasma against the infecting organism. That was true in this case; the patient had a titer of 1:350 or higher against the O antigen of *Esch. coli*.

In regard to the cortisone, I am not entirely clear as to why this was given, especially since steroids are known to be capable sometimes of enhancing infection. I suspect that the rationale was one of the following: (1) cortisone was given with the hope that it would cut down the amount of reaction on the valves and that in this way the organism would not become covered over with fibrotic tissue and became protected against the antibiotics. (2) The physicians were considering the possibility that the patient had some kind of adrenal insufficiency, but I see no evidence of this condition. (3) Cortisone was given to counteract the marked loss of electrolytes, particularly sodium chloride.

Now let us look at the complications. The overwhelming yeast infestation that appeared at the end I do not think is surprising. Secondary fungus infections are one of the recognized risks of antibiotic therapy; they occur most commonly with the broad spectrum antibiotics. This patient certainly had plenty of antibiotics to explain this unhappy development.

The second complication is the development of hypochloremic alkalosis, with a decrease in serum values of almost all electrolytes. This could be due to some renal damage (even though the urines were negative) due to the *Esch. coli* toxins. I doubt that the patient had any primary kidney disease. The most common cause for hypochloremic alkalosis is excessive vomiting or sweating.

DR. ROBERT HAGERTY.—There was diarrhea at the time, but it was not

excessive, and with the first drop in electrolyte levels, no diarrhea was present.

DR. MASSELL.—Such an episode might explain some of the lowering of the potassium. It is to be noted that the electrolyte changes, particularly the low calcium and the alkalosis, could well explain the tetany that developed at one point as well as the electrocardiographic changes.

The last complication that should be mentioned is the thrombocytopenic petechial hemorrhages. I understand from what Dr. Diamond has written that this commonly is secondary to infection. I assume that in this case we are dealing with a secondary thrombocytopenia, resulting from the infectious process.

In conclusion, then, my final diagnosis in this case is that we are dealing with an *Esch. coli* septicemia due to an *Esch. coli* endocarditis. Regarding the question of the underlying cardiac condition, there are a number of possibilities that I have mentioned; my first choice is a bicuspid aortic valve; second, no underlying heart disease; and third, other types of congenital defects. Rheumatic heart disease I would put down at the bottom of the list and I would put congenital endocardial sclerosis far, far down at the bottom of the list. Finally, although there is no evidence of this complication in the clinical protocol, it is quite possible that autopsy may reveal metastatic abscesses due to the infecting organism.

DR. CRAIG.—Dr. Neuhauser, would you like to show the x-rays now.

DR. E. B. D. NEUHAUSER.—In the initial chest films, the heart appears surprisingly normal, both in size and contour. There is no abnormality of the great vessels and the intrapulmonary vessels appear to be of normal caliber and distribution. At that time though, there is considerable enlargement of the liver, each kidney is considerably increased in size. The spleen is larger than normal. What this indicates, of course, is open to interpretation; whether it is a nephritis, splenitis, or what, we had only this one examination of these organs. Later on, during the course of serial chest films, I think, at least once, there were small punctate, cone-shaped areas of increased density at the lung base. On careful retrospective search we could detect no localized areas of pulmonary radiolucency, which are the earliest signs of pulmonary infarction.

On the final examination, the heart is increased in size; it has become more nonspecific in contour. It has lost, to some extent, definitive chamber configuration. I think there is a definite diminution in the size of the intrapulmonary vessels when this picture is compared to the initial one. There is no great increase in the size of the heart, although it perhaps measures a centimeter larger in the single transverse diameters seen here, and still at the last examination the abdominal organs are increased in size, but have evidently not changed very much since the first examination a month previously. So I think in retrospect we have evidence of a heart that is essentially normal in size and contour, with normal vessels, normal lungs, which later develop well-defined areas, probably lobular in distribution, of increased density. On the last examination the heart has increased in size,

has lost chamber configuration, and there is diminished vascularity throughout the lung.

DR. GUNTHEROTH.—It was not mentioned, but this boy did have a pericardial friction rub at one or two times in his hospital course here. The diastolic murmur was very well localized at the lower left sternal border, suggesting tricuspid involvement rather than mitral.

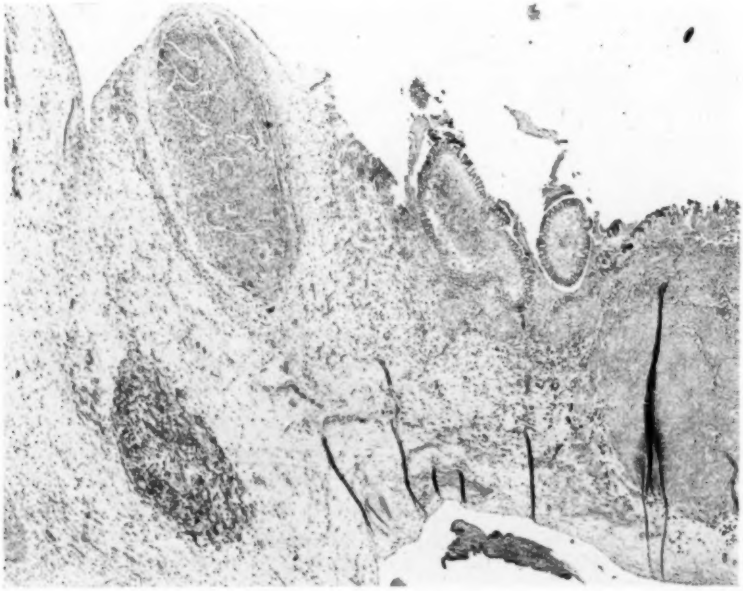

Fig. 1.—Photomicrograph, heart. The right ventricle papillary muscle showing the broom straw adjacent to a large thrombus on the right. (Hematoxylin and eosin; ×30; reduced ⅓.)

DR. MASSELL.—It would be rather difficult to diagnose tricuspid disease, unless he had a congenital tricuspid lesion; it could be rheumatic tricuspid stenosis, but at this age or any age tricuspid rheumatic involvement is very rare. I would prefer an atrial septal defect than tricuspid valvular involvement. Patients with tricuspid disease who have endocarditis on the right side of the heart often will have no peripheral emboli. That might be important. But these individuals often do not have positive blood cultures either.

A PHYSICIAN.—I would like to ask about the use of antibiotics; the doses seem very large.

DR. JANEWAY.—We gave larger doses to this patient than to any before or since.

DR. CRAIG.—The child did have a quite generalized rash and numerous areas of nonconfluent petechiae. He had tremendous ulcerations about the buttocks and diffuse purpura associated with his thrombocytopenia. The lesions of the skin had numerous yeast forms growing in them.

The point of most interest was the heart. In the right atrium, just above

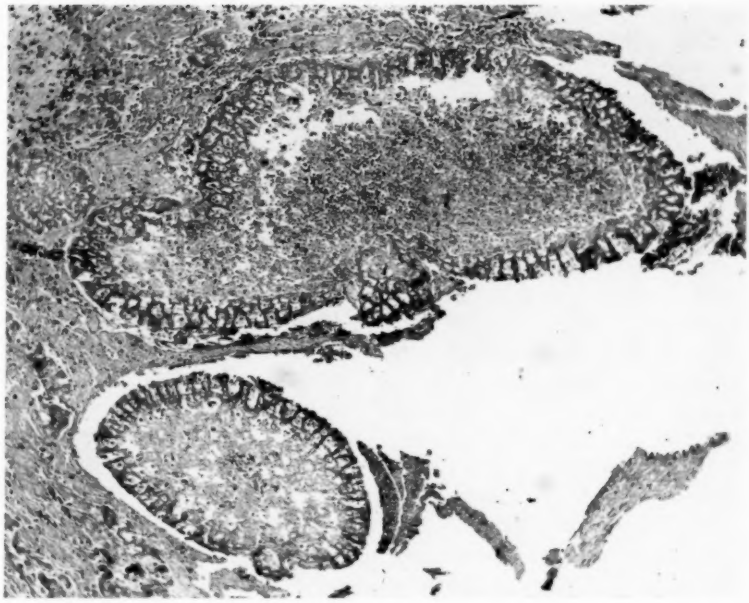

Fig. 2.—Photomicrograph, heart. Higher power of Fig. 1 to show the structure of the straw in situ. (Hematoxylin and eosin; ×100; reduced ⅛.)

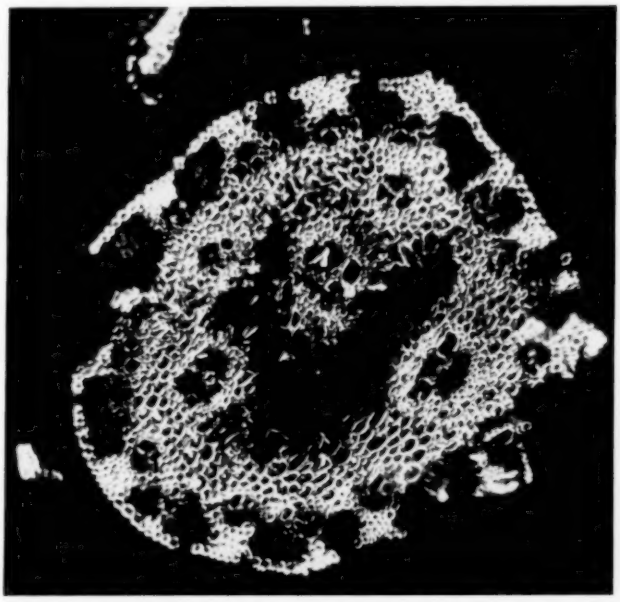

Fig. 3.—Photomicrograph, broom straw. A cross section of the broom straw under polarized light. (Unstained; ×130; reduced ⅛.)

and attached to the tricuspid valve was a large thrombus, and right at this point there was a small straw that passed through this large thrombus and embedded itself below in the papillary muscle (Figs. 1 and 2). Like all good pathologists, we took a section of it. It had the appearance of a quite typical dicotyledonous plant (Figs. 2 and 3). It did not have the cambium layer that one expects on a monocotyledonous plant. We believe this to be a broom straw made of corn stalk. The huge thrombus in the right atrium was completely unorganized and we could find no bacteria in it. Our cultures of the thrombus yielded *Candida albicans* and an enterococcus. I suspect the latter was a contaminant. Cultures of both lungs, the spleen, and the heart's blood, all grew *C. albicans*, although we were unable to find any systemic evidence of Candida outside the superficial involvement in the tongue and skin. There were very few evidences of embolization or infarction in the lung. We found only one thrombus in a large vessel, associated with an area of acute hemorrhagic infarction of the lung. There were no areas of organized emboli or old infarction; this correlates well with Dr. Neuhauser's findings on x-ray. In general, the lymphoid tissue was greatly depleted throughout the body, partly, I suppose from inanition, but a good deal of it must have been due to the cortisone. In the spleen there was tremendous congestion and almost complete depletion of the lymphoid follicles. No abscesses were found. The liver had a good deal of congestion, due in part to obstruction of flow from the right atrium into the right ventricle. The kidneys were twice the normal weight, and had greatly swollen and very pale cortical areas. The medullary areas were intensely congested and somewhat sunken beneath the other areas. No obvious microscopic lesion was found. We wondered about polymyxin and its effect on the kidney, but we could find none of the changes that are described in the literature. There was slight swelling of the tubular epithelium, and dilatation of the tubules, but we did not feel that we could ascribe any of these changes to polymyxin.

We were unable to trace the course of this small broom straw that lay in the heart from either the esophagus or the stomach. There was no evidence of attachment or fibrosis in either area, nor was there evidence of an abscess.

DR. MASSELL.—I think this is an amazingly interesting case. I could have been smarter in making the diagnosis, especially on the clue that Dr. Guntheroth gave together with the fact that there were no peripheral emboli.

DR. JANEWAY.—What is your impression of the cause of the kidney disturbance?

DR. CRAIG.—We suspect the polymyxin, but we cannot prove it. I would expect more fat in the renal tubules if such were the case.

In cattle this invasion of foreign bodies to the heart from the stomach is a quite common occurrence, the reason being that in their usual position on four legs, the second stomach lies mostly inferiorly, so that every heavy object tends to gravitate toward the bottom, and the movement of the heart and diaphragm gradually wears the wall away and they get a peri-

carditis, and, not infrequently, involvement of the heart itself by foreign material.[3] I read in a recent issue of the Sunday *New York Times* that cattle are now fed small magnets to prevent stomach perforation by iron-containing materials.

As one wit said of this case, "I think we should say that this is truly the last straw."

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# Pediatric Profiles

## *Luther Emmett Holt*

*(1855 - 1924)*

IN PREPARING this "profile" of the famous pediatrician, L. Emmett Holt, Sr., we have considered our contribution to be personal recollections and impressions, our own and those of others close to him. One of us (H. H. M.) was the last of a series of five office assistants of whom John Howland was the second; both of us were his pupils at the College of Physicians and Surgeons, New York City, in the years 1904 and 1905 and both became members of his department, though not assigned any real responsibilities. Not many are now living who have been intimately associated with Dr. Holt or seen him in action. Although a biography by R. L. Duffus and L. Emmett Holt, Jr., gives a vivid picture of the man and of his activities and achievements, an inclusion of a biographical sketch in our "profile" is necessary, not only for completeness but also as a background for the personal experiences we have to offer. We have drawn on this official biography as freely as if we ourselves had been the authors.

### BIOGRAPHICAL SKETCH

Luther Emmett Holt was born in Webster, New York, March 4, 1855, the youngest of three children. His ancestor, Nicholas Holt, came to this country fifteen years after the arrival of the *Mayflower* and settled in Andover, Massachusetts. Nicholas' grandson, Abiel, moved from Andover to Windham, Connecticut, and Abiel's son, Nathan, followed the western movement to Willington, Connecticut. Constant, Nathan's grandson and Emmett's grandfather, proceeding in an oxcart with his bride and worldly possessions, settled in Webster, near Rochester, clearing the forest and building a log cabin. Here Horace,

Emmett's father, was born. Emmett's mother was Sabrah Curtice, whose ancestors also arrived in this country from England in 1635 and settled in Sudbury, Massachusetts. Her great-grandfather fought in the American Revolution. Her grandfather, Ebenezer Curtice, at an advanced age moved from Amherst, New Hampshire, to Webster, where his son Ziba, Sabrah's father, was born. We have given these details to bring out that, although born in western New York, Emmett Holt was of pure New England ancestry, as indeed the biblical given names indicate vividly enough, because that Puritan origin gives the key to his character. Like so many others of that stock, who have done important service, he was driven ceaselessly by a stern, unremitting, somewhat somber sense of duty, with thoughts and activities, however, confined in a sharply circumscribed area of life.

Emmett's father, Horace, had become the possessor of a well-developed farm where he lived in comfort and appears to have been a solid, successful, respected citizen of Webster. His mother, entirely self-educated, was obviously a remarkable woman, so resembling her son in feature and qualities of mind, as judged from photographs and letters, as to cause one to attribute much of his inheritance to her. Her letters to her son were marked by the same concern for the development of character which is in turn to be found in his letters to his children. She wrote: "I never want my children to do anything that is right and for their improvement by the halves; I should very much dislike to have either of my boys attempt anything and fail." The relations between Emmett and his mother were the closest possible; she emptied her heart to him unreservedly and he in turn laid bare to her the minutest details of his life.

Both his parents were ardent Baptists. "Emmett," his mother wrote, "when you choose a wife, I do hope you will get a Baptist. As you prize your everyday Christian life and Christian usefulness, pray much over this subject now before your affections are so tested as to blind your better judgment." In a subsequent letter, jumping to the practical, she advised him, "Don't look for a mature woman of 40 in a girl of 20, and we can't find perfection in this world." When Emmett did choose a wife, she was a Baptist, but the reason was circumstance rather than obedience. When he announced his engagement to his mother, she replied, "I will not feel that she has robbed me of my place in your heart, but that God has given her a place a little nearer."

To know that a celebrated man was once a simple child is comforting. In a letter of reminiscence, written in 1906 by Eliza, Emmett's older sister, we find, ". . . when you came on the stage, you were always greeted with applause and audible whispers of 'ain't he cute.' Don't you remember 'The Pickets' that Curt and Zibe sang the night you sang 'Little Sam' or 'Goodbye Jeff!' (Jefferson Davis)."

Emmett was educated at the District School and then at Webster Academy. At the age of 16 he entered Rochester University, where the curriculum included a course on the 241 bones of the human anatomy! Young Emmett graduated seventh in his class. After graduation he taught at Riverside Academy, Wellsville, N. Y., but during that year decided to study medicine

for reasons not clear, in 1876, aged 21, entering the Medical College of Buffalo University. At the end of a year there the first great deciding event in his career occurred. At the Ruptured and Crippled Hospital of New York City, a vacancy opened for a student intern at an annual salary of $400. The position was offered to a Rochester youth who declined it. Emmett, perceiving in it the opportunity to transfer to a better medical school, the College of Physicians and Surgeons, New York City, secured it, registering there and taking up his duties at the Ruptured and Crippled Hospital in February, 1878. The experience at this hospital proved a vital turning point in his career. It was there that he fell under the guidance of Virgil Gibney, soon to become Professor of Orthopedics at the College of Physicians and Surgeons in New York City, who early came to realize the abilities of his young friend and became his sponsor. It was to Virgil Gibney that in gratitude Holt later dedicated his famous textbook. But far more important, at the Ruptured and Crippled Hospital, as a lowly subordinate, he was thrust in contact with sick children, and was left free to observe and, as he became more experienced, to take full responsibility for them during illness of a medical nature. It was this taste of pediatrics, while a student, which determined the direction of his career. He graduated from the College of Physicians and Surgeons in 1880, aged 25 years, among the first ten in his class. His graduation thesis, evidently stemming from his experience at the Ruptured and Crippled Hospital, was "Articular Osteitis of the Hip Joint."

His high standing at the College of Physicians and Surgeons gave him claim to an internship at Bellevue Hospital and he chose surgery, planning on a surgical career. Although out of line with his subsequent development, his year at Bellevue with its Department of Pathology the foremost in the country must have been a broadening experience, especially as he was there thrown in contact with that nucleus of progressive young men, a little older than himself, who were about to start a new era in medicine in this country, notably William Welch, William Halsted, and Edward Trudeau. The acquaintance with Dr. Welch was to prove of importance subsequently. During the course of the internship Holt evidently decided that surgery was not his métier, for at its expiration in 1881 he opened his office for the practice of medicine in New York City at 200 West Fifty-second Street. It was during the first year of practice that he resolved to devote himself to pediatrics. Since pediatrics as a specialty did not then exist, his plan was to practice general medicine with as much cultivation of pediatrics as the former would admit. Actually during this period he included obstetrics and minor surgery, in particular tonsillectomy performed in the home. He did not succeed in freeing himself from his bondage to general medicine until a little after 1891, a period of ten years, when he stopped taking new adult patients. Shortly after opening his office, he started a "quiz," or tutoring class, for medical students, as both Dr. Welch and Dr. Halsted had done before him. He also obtained a staff appointment at the Northwestern Dispensary, where there was a pediatric clientele.

And now the second opportunity of his medical life opened. He was offered and accepted the service at the New York Infant Asylum, situated at Mount Vernon, an hour away by train. No one else wanted to bother with it because of its distance, but Holt with his superior vision perceived its latent possibilities; there he would have a children's service of his own the year round and, with that in view, time was not an obstacle. The hospital contained 300 beds. The intern was Charles G. Kerley, later to become the fashionable pediatrician of New York City and himself the author of a textbook on pediatrics dedicated to Holt. Young Holt remained in charge of the pediatric service at Mount Vernon for eight years. It was during that period, in which he had complete freedom to observe at the bedside and autopsy room and to put his therapeutic ideas to trial, that he laid the foundations of his pediatric knowledge. As his experience grew, he began to publish articles and to establish himself, in the New York City world at least, as a rising young authority on children.

By 1884 he had saved enough money to go to Europe, and traveled through Belgium, France, Germany, Austria, Switzerland, and England, and made his first direct acquaintance with the French and German languages. From Vienna, encountering students from eleven different countries, he wrote his family: "It seems like a veritable tower of Babel discussion to hear them all talking before the lecturer comes in. You think what a plain, clear, wholesome language English is and wonder they do not all learn it and stop their senseless jabbering." The transformation of this "i n n o c e n t abroad," as his biographers then describe him, to the urbane, spick and span, remote Professor Holt, seems nothing short of metamorphosis. What he obtained from his trip to Europe was a vision of a "new planet swimming into his ken" which had existed there only dimly, if at all, a new world of art, culture, history, and also of medical knowledge and progress which he must have realized were far in advance of ours.

Pediatrics was now developing apace in this country around such men as Jacobi, Chapin, O'Dwyer, presently to develop intubation, Koplik, Rotch, Keating, the compiler of the *Cyclopedia of Diseases of Children* to be published in 1890, and others. Of this group Jacobi was the center and also the oracle with about him something of the "When I ope my mouth, let no dog bark." Young Holt was at this time not a leader but rather a rising industrious young man of promise. That he was being recognized in pediatrics was shown by his inclusion as one of the editorial board of the newly organized Archives of Pediatrics, started by a New York City group in 1884 as the first pediatric journal in this country and his reputation was mounting steadily. In 1887 the American Pediatric Society was formed. It is doubtful if Holt was one of the original organizers, but the following year, when the first meeting occurred, he was one of its forty-three charter members. In 1889 he relinquished his service in Mount Vernon and accepted in its place attending services at the New York Nursery and Child's Hospital and the New York Foundling Asylum.

Now came the third great event in his professional career, namely, the opportunity to become physician-in-charge of the almost defunct Babies Hospital. In connection with this and the student internship at the Ruptured and Crippled Hospital as well as the service at Mount Vernon, we have used the word "opportunities," and so they were, but only for the reason that he made them such. To most young physicians they would have been gateways to nowhere in particular, or at most to the routine experience of "Main Street." But like Beaumont, when faced with the accident of Alexis St. Martin's wound, Holt had the vision to perceive the ultimate possibilities and the ability and energy to realize them. The Babies Hospital was in danger of foundering; if he could succeed in building it up, he would have his own hospital near by in which he could carry out his ideas under conditions which he, himself, could control. Perhaps, too, the fact that the Babies Hospital was in dire straits appealed to his Puritan sense of duty. In any event, he accepted the offer and went at the problem of its reorganization with all the energy and resourcefulness of his nature. He saw exactly what it was necessary to do. The result of his acceptance as physician-in-charge was that presently he soared like a rocket high above his colleagues to his position of supreme eminence in pediatrics in the United States.

In 1889 the Babies Hospital, founded by Drs. Sarah and Julia McNutt, was in danger of going under for lack of funds, without an attending physician or permanent home. Holt was called in. "He took the hospital as it was, shaped it according to his own vision and gave it life. From 1889 to 1923, when he left for China, he lavished upon it literally a parental care. It was in every sense of the word his creation—its finances, its brick and stone, its administration, its medical policies, research and teaching. His first step was to secure financial backing. Selected individuals were persuaded to go on the Board of Trustees. Its first home, a converted dwelling house on Lexington Avenue, was expanded and in 1901 the hospital was transferred to a modern seven-story building with outpatient facilities, laboratories, and 70 beds, on the corner of Fifty-fifth Street and Lexington Avenue." Under his guidance it became the most celebrated pediatric hospital in the United States.

His first burst into fame—and it really was a burst—came about in the most curious way. With the limited funds available at the Babies Hospital the problem of obtaining adequate nursing seemed insoluble. Mrs. Chapin, the wife of Dr. Robert Chapin, suggested that with a minimum of expense young girls could be obtained to serve as nursery maids, working under the direction and teaching of resident nurses, and that, if they were given adequate training and a diploma, they would be in demand. At the outset selected girls were given a four-month course, later increased to six months, with instruction in infant feeding, care, and nursery hygiene. The demand for these nursemaids soon exceeded the supply. In order to make their training more efficient, Holt prepared "A Catechism for Nurses" in which questions were asked and answered about

clothing, bathing, feeding, sleep, fresh air, etc. There were twenty-three questions and answers. "The nurses studied the catechism and when they graduated took it with them. There followed requests for copies from their employers and the supply was soon exhausted. . . . The catechism was expanded and in 1894, *The Care and Feeding of Children* made its appearance in a booklet of 66 pages." The biographers say ". . . probably no one would have been more surprised than Dr. Holt or his publishers had they been told that they were launching a volume that was to go through 75 printings and which was to be translated into Spanish, Russian and Chinese." The *New York World* wrote, "If women were not permitted to marry until they could pass a fair examination in this short catechism of 60 pages, the death rate would be decreased at least one-third." In time the booklet was expanded to some 200 pages and underwent twelve revisions during the author's life. It is interesting that Holt's fame first sprang from the lay public.

In 1891 Holt was appointed Professor of Pediatrics at the New York Polyclinic Hospital and Medical School, where he had taught in a minor capacity for some time.

In this year the Rockefeller Institute was founded. Mr. John D. Rockefeller was a member of the Fifth Avenue Baptist Church and there Holt had become intimately acquainted with the Rockefeller family. Dr. George Corner, historian of the Institute, informs us that the credit for the proposal to Mr. John D. Rockefeller to establish the Institute goes to Mr. Frederick T. Gates, his advisor and close friend. Three years afterward, John D. Rockefeller, Jr., happening to be traveling on the same train with Holt, fell into conversation regarding the project. Holt, illustrating what such an institute could accomplish, citing among other discoveries diphtheria antitoxin, is thought to have convinced young Mr. Rockefeller then and there to go ahead. At a dinner at Holt's home three weeks later, at which Mr. John D. Rockefeller, Jr., was present, the project was developed in detail. The initial donation of $200,000 for the Institute was addressed to Holt. He was selected as a member of its Board which was composed of as distinguished a medical group as this country could boast, including besides himself, William Welch, Mitchell T. Prudden, Theobald Smith, Hermann Biggs, Christian Herter, and Simon Flexner.

Holt determined to write a textbook on pediatrics as far back as 1890 and he had begun work on it then, but it was not completed until 1897. Rotch of Boston had published his *Pediatrics* one year previously, written as a series of lectures. Whatever the merit of its substance, the style of Rotch's book was pompous verbosity. It ran through five editions, the last in 1906. Holt's book, on the other hand, in simple clear language, was at once recognized in this country as the standard text on pediatrics, occupying a place corresponding to Osler's textbook on internal medicine. All medical students were given it to study and it was the pediatric reference book for all practitioners. During Holt's lifetime, in successively revised forms, it ran through eleven editions and was translated into Chinese!

In recognition of his achievements, in 1897 Holt was made the president of the American Pediatric Society. He was then 42 years old and at the very height of his career.

Together with others, Holt was much concerned over the poor quality of the milk supplied to New York City and played a prominent part in the campaign for clean milk. Under a grant from the Rockefeller Institute he had made studies in the tenement districts of New York City to prove that milk with very high bacterial counts was related to infant morbidity and mortality and we recollect his apparent disappointment, when he discussed the results before us students, that the outcome did not show the relationship more decidedly. He was one of the prime movers in working out the code for clean milk production which is now so accepted as standard as to be taken for granted: cleanliness in the barns, health inspection of cattle, physical examination of employees, cleanliness of milking conditions, immediate cooling and bottling, and regulations covering the bacterial count of the final product. The result of the efforts of the group of workers, of whom Coit of Newark was the leader, was the establishment of as nearly a perfect raw milk as could be obtained, known as "certified milk." Later in New York City the milk was graded into Classes A, B, C, et cetera, according to the degree of its conformity with the standards. The establishment of milk commissions and advisory boards to the New York City Health Department followed. The pioneer work, aiming at "pure milk" production in New York City, spread over the country.

The Walker-Gordon Laboratory with its contributory farm was originated in Boston by Rotch with a twofold object of furnishing a station where milk of the first quality could be obtained but, even more important, where the intricate formulas of the percentage system of milk modification could be compounded from prescriptions sent in by the pediatricians exactly as prescriptions are filled by pharmacists. Holt, who had adopted the percentage system of infant feeding, saw the value of the laboratory, and with a few other New York City physicians provided the money necessary to establish a branch in New York City. We recall it well, situated on Fifth Avenue not far from Forty-second Street, with glass windows extending all across the front which furnished a complete view of the interior. Passersby used to stop to see what was going on inside and we students almost always loitered for a moment in passing. The floors were kept flooded to avoid dust, and three men wearing masks, in white suits and rubber boots, could be seen at laboratory tables squirting milk from burettes into baby bottles. We students were sent in squads by Holt to visit the laboratory and remember being much impressed when we were given tastes of raw milk which had remained sweet after a voyage to Europe and back. When the percentage method of feeding died out and pasteurization was applied generally to all milk, including certified, the Walker-Gordon Laboratories, which at their zenith had spread to a dozen or more of the big cities, for the most part went out of existence. But in their time they exerted a great educational influence by demonstrating

what perfection in production can result from relatively simple sanitary procedures.

In 1901, when Holt was 46 years old, he resigned from his professorship at the New York Polyclinic to become the Professor of Pediatrics at the College of Physicians and Surgeons, succeeding Abraham Jacobi.

In 1903 Holt went abroad for the second time, no longer unknown but as a prominent American pediatrician with European reputation. He there met Baginsky, Schlossmann, and others in Germany and Austria and made the acquaintance of the most prominent British physicians of the time. Everywhere he was entertained royally. In London he visited Still and formed a permanent friendship with him, but he was especially attracted to John Thomson of Edinburgh. Thomson was a remarkable observer and utterly delightful in his simplicity and kindness. Holt entertained the greatest admiration and feelings of kinship for him. In 1908 he again visited Europe on the occasion of the Sixteenth International Congress of M e d i c i n e where he was generally recognized as the leader of American pediatrics.

Holt was on the Board of Directors of the Henry Street Settlement, giving them advice on nursing problems, and was continually in demand for counsel in regard to movements of various kinds for the promotion of health in children.

In 1919 at the close of the First World War he was one of the delegates to the Red Cross Conference at Cannes. Actually it was he who was responsible for the development of the child welfare program adopted by the conference.

In the last four and one-half years of Holt's life his time and interest were largely taken up with the Child Health Organization, the presidency of which, after some hesitation, he had accepted. The project adopted by the C.H.O. was so bizarre that a brief explanation is required. The C.H.O. sprang out of the revelation of the deplorable physical states of the draftees in the First World War and its object was to prevent similar conditions from developing in oncoming children. The program was an educational campaign of pure propaganda on a nationwide scale, such as now would be conducted by television. The daring, and at the time original, plan was developed by Sally Lucas Jean. In brief, it was to tour the country with a troupe of itinerant players, Cho-cho, a clown, a nurse in disguise as the "health fairy," a ventriloquist, a magician, et cetera, all ingeniously converting the interest won by their tricks and subterfuges into health instruction. An exhibit was the "Healthland Flyer," a miniature train which could carry passengers on a miniature railroad with stations at "Milkville," "Toothbrush Junction," et cetera. The organization visited schools, fairs, exhibitions, et cetera, throughout the country and produced sensations e v e r y w h e r e. Enough has been said to show the general nature of the venture.

A pure propaganda campaign, such as just indicated, seems more in keeping with lesser personages than Holt, especially as its benefits could not be checked, but it was perhaps, after all, in character. Holt's interest in parlor games was well known and it has been suggested to us that the fascination of this educational campaign was that of

a gigantic game with the future health of a nation the goal. William Welch exclaimed, "What fun Holt is having with this new toy of his!" Holt most certainly believed it was worth while. At any rate this apparent departure from the beaten path into the somewhat misty open spaces indicates how far Holt's interest had extended into preventive medicine. It had been perhaps stimulated by the Red Cross Conference at Cannes where the child health problems considered belonged to the world.

The American Association for the Prevention and Study of Infant Mortality had been founded in 1910 and Holt had made two addresses before it. In 1918 its name was shortened to the American Child Hygiene Association. In 1923 this and the C.H.O. were combined into the American Child Health Association with Herbert Hoover as President.

In 1921 Holt gave the Lane Lectures under the auspices of Leland Stanford University. In an expanded form these were published in a book entitled, *Food, Health and Growth*. In this year, at the age of 66, he resigned from his professorship at the College of Physicians and Surgeons.

In 1923 he was elected for the second time president of the American Pediatric Society, an honor which had previously been accorded only to Jacobi. Holt made a memorable valedictory address on the occasion, "American Pediatrics, a Retrospect and Forecast." In it he emphasized the future role of the pediatrician as a health teacher. "Nowhere in the whole realm of preventive medicine is there such a field of usefulness as that which is open to the pediatrician."

In the summer of 1923 he went as visiting professor to the Peking Union Medical College and died in China as a result of coronary disease on January 14, 1924, at the age of 68 years.

Holt was treasurer and vice-president of the New York Academy of Medicine, twice refusing the presidency, a director of the Henry Street Settlement, a member of the National Child Labor Committee, a member of the Advisory Board of the New York Health Department and of the Advisory Council of the Milbank Memorial Fund. He was a founder and one of the original editors of both the *Archives of Pediatrics* and the *American Journal of Diseases of Children*. In 1902 he was given the degree of LL.D. from Rochester University, of which he was a trustee and close advisor to the President. Both Columbia University (1904) and Brown University (1914) gave him the degree of D.Sc.

### HOLT AS A TEACHER

Holt was small and spare, weighing about 135 pounds, 5 feet 6 inches tall. When we were his students, his abundant dark brown hair had become heavily lined with gray. It was parted exactly in the middle, so perfectly that it was difficult to imagine that a single hair could be out of place. His features were regular and well formed, but not conspicuous except for a rather unusually resolute mouth. His expression was at all times peculiarly alert; his glances and movements were quick. He was always quietly but immaculately dressed and at any moment might have stepped out of a fashion plate. When he spoke, it was with a quiet but clear voice, in short incisive sentences, without hesitation or repetition. He did not laugh or

smile; his manner was more than serious, it was earnest. There was nothing about him which could be called impressive, due perhaps to the absence of any outstanding feature; rather he appeared a highly efficient, perfectly coordinated human machine. He seemed to us austere and unapproachable; we were in awe of him. We realized that he was a distinguished man, because we were told so, but had no idea that he was by far the most distinguished man in the entire medical faculty at the College of Physicians and Surgeons.

Holt was a born teacher. As pointed out already, he taught school for a year before entering medicine, and soon after he received his degree at the College of Physicians and Surgeons opened a quiz. On his first voyage to Europe, when a young bachelor, he organized a class in physiology, composed of young ladies aboard! In his earlier years in New York he conducted a Bible class at the Fifth Avenue Baptist Church where one of his pupils was Linda Mairs whom he subsequently married. His famous *Care and Feeding of Children* was written for the education of nursery maids, and his classic, *Diseases of Infancy and Childhood,* for the instruction of students and physicians. Letters to his children were sprinkled with didactic advice.

Holt's teaching of medical students took the form of formal lectures held in the amphitheater of the College of Physicians and Surgeons, formal clinics at Vanderbilt Clinic, and informal clinics before successive sections at the Babies Hospital, or occasionally at the New York Foundling Asylum. We can dismiss his formal lectures briefly, for they were restatements of the chapters in his book. We doubt if an author who has developed pathways through the maze of a subject can avoid traversing them over again. Except for the presence of Holt himself and relative emphasis placed here and there and an occasional interpolated personal experience, one might just as well have spent the time on the book. The lectures spanned the entire subject of pediatrics and were accompanied by assignments of reading, so that by the end of the year the entire book had been covered. Since they were delivered at the College, they could not be illustrated by patients, though we recollect that a baby with whooping cough was placed in a high chair on two different days with the expectation that he would whoop—he was perverse—and occasionally a child with some condition which was visible from all parts of the amphitheater, for example, eczema, might be placed on exhibit. A large part of the lecture course was devoted to the percentage method of infant feeding, to be discussed presently.

The formal sessions at the Vanderbilt Clinic, at which the entire class was present, were splendid performances, for they gave Holt the opportunity to demonstrate his methods. If the mother was present, he questioned her himself, exploring the developmental history with the greatest care and evidently acutely aware of its importance, and inquiring into the feeding in the minutest detail. For example, was the cereal cooked and how long, how many slices of bread were eaten at a meal, was the bread fresh or stale, how much butter, and he invariably probed eating between meals. He tested the mother's veracity by catch questions. Before he

performed a "physical," he invariably weighed and measured the child and regularly determined before us the developmental status. His history taking and examination were models of system, thoroughness, and completeness; no detail too small to be unimportant and neglected.

The informal clinics, held before small sections, were different. The children selected were from the wards. A student was assigned to the patient and had the opportunity the day before to read a specially prepared abstract of the history and to perform a physical examination. He would present the case before the group and, on Holt's question, "Doctor, what is your diagnosis?" give it and outline his treatment. Holt would then ply him with questions, often leading toward pitfalls, designed to test his observations and thought. The questions were practical, directed to bring out some useful point, impersonal but kindly. Prognosis was never neglected.* As we look back on these clinics, conducted in the Socratic fashion, they were rarely equaled.

Since in his informal clinics Holt was able to select his subjects, it is interesting to note his choices. They were diseases and conditions most commonly seen in pediatric practice: vomiting and diarrhea, malnutrition, thumbsucking, habit spasms, enuresis, convulsions, eczema, congenital syphilis, diaper rashes, impetigo, pneumonia, croup, etc. Scurvy, then recently recognized, was a rare tidbit, as it has been to teachers ever since. Rickets was also a favorite. Diphtheria and the exanthemas were taught by one of Holt's assistants at the Willard Parker Hospital. Holt seemed to us students to be interested in disease exactly in proportion to its frequency, not in diagnosis per se or in rare diseases. For example, in congenital heart disease his teaching was concerned chiefly with differentiation from acquired heart disease and with the prognosis; he did not seem interested in speculation regarding the kind of malformation, and never chose cases because of their dramatic interest or to show off. Although his interest appeared to us students to be limited to the clinical aspects of illness, the biochemical studies, later to be mentioned, showed that actually it was deeper than that and that his teaching was governed by what his conscientious mind thought most important for us to know.

Some general characteristics of Holt's teaching must be pointed out. One was his habit of summing up his experience in the form of aphorisms or rules of thumb. For example, bleeding from the nose in the young child should always suggest nasal diphtheria, congenital syphilis, or foreign body in the nose. Evidently, whenever possible, he sought to establish signals which automatically turned on useful associations or sequences of thought. He was extremely fond of statistics, in particular those relating to morbidity and mortality. The incidence of bronchopneumonia as compared to lobar pneumonia and the frequency of lobar pneumonia in the right lower lobe as compared to the left concerned him.

A teacher never really knows what he teaches. Evidently what Holt thought he was teaching us was facts, all that were necessary for us to know, marshaled, bristling, and in order. He certainly did succeed in this, and

*Often he pointed out to us students that private practice was where one learned prognosis. When one of us worked as a student at the Babies Hospital in 1903, Holt had an envelope placed at the head of the bed in which each member of the staff was required to enter his prognosis in writing.

we do not wish to belittle its value. But what he taught in addition—and it was much more important—was himself; thoroughness, accuracy, adherence to system, attention to detail, intellectual honesty, the sacredness of the obligation of physician toward patient.

### HOLT AND PERCENTAGE FEEDING

Since in our time at least the percentage method of infant feeding was almost a gospel in Holt's teaching, it is important to understand his part in its development and the evolution in his attitude regarding it. The method had its origin in the conception of the German pediatrician, Biedert,* that casein of cow's milk was its indigestible element and that this was the essential cause of the inferiority of cow's milk as an infant food. As originally conceived, the object of the percentage method was imitation of human milk. If the protein in a cow's milk mixture could be reduced to the percentage in human milk, the casein would fall, it seemed plausible to think, below its toxic level. The trick of "humanizing" cow's milk was dilution of cream with water and addition of sugar; the dilution, if properly adjusted, brought the protein to the desired low level; the cream, if correctly selected in view of the dilution, yielded just the required fat percentage and the sugar could be raised to 6 or 7 per cent by addition.

The method of compounding, just described in principle, was developed in Germany by Biedert* and others, certainly by 1894, for in that year Gärtner† published a method for commercial production of such a human milk imitation. Actually in 1863 Ritter von Rittershain* advocated diluted cream with the addition of lactose as the best feeding for rachitic children, commenting that the resultant mixture was similar in composition to human milk. He pointed out, also, at this early date that by using cream the casein would be reduced, holding that the latter was the indigestible component of cow's milk. In these conceptions, which lie at the bottom of the percentage method of cow's milk modification, von Rittershain anticipated Biedert by many years.

Whether Rotch of Boston, who had studied in Germany, conceived the idea independently or imported it is unimportant, but he was the first to set it in operation in this country and remained its high priest to the end of his life. Certainly by 1894 Holt had accepted the percentage method as a notable advance in artificial feeding. However, his contribution to it, not published until 1901, was a small one, merely the simplification of formula production for the home. He did this by making use of the cream rise in the ordinary quart bottle and by confining directions to 20 ounce volumes. The upper one-third of the quart bottle of average dairy milk contained approximately 10 per cent cream. By diluting 7 ounces of this with 14 ounces of water and adding 1 ounce of sugar, the 3 per cent fat, 6 per cent sugar, and 1 per cent protein (the "3-6-1") imitation of human milk was obtained; and by taking 10 ounces from the upper half of the quart bottle, which latter was 7 per cent cream, and adding an equal part of water and 1 ounce

*Biedert, P. H.: Die Kindernährung im Säuglingsalter und die Pflege von Mutter und Kind, ed. 3, 1897, Ferdinand Enke.

†Gärtner, G.: Ueber die Herstellung der Fettmilch, Wien. med. Wchnschr., p. 1870, 1894.

*von Rittershain, Ritter: Die Pathologie u. Therapie der Rachitis, Berlin, 1863, August Hirschwald.

of sugar, a 3.5 per cent fat, 7 per cent sugar, and 1.7 per cent protein was the result. These are merely two examples.

Now for Holt's teachings: In the first edition of the *Care and Feeding of Children*, 1894, he advocated the "3-6-1" imitation of human milk for all infants. He must then have thought percentage imitation the solution of artificial feeding. In the second edition, 1900, the recommendations for cow's milk feeding had become both elaborate and specific. Five modifications were to be used in succession: Formula I from the third to the fourteenth day; II, from the second to the sixth week; III, from the sixth to the eleventh week; IV, from the eleventh week to the fourth month; and V, from the fourth to the tenth month. These formulas were all cream mixtures, the first three, derived from 10 per cent cream, having the proportions of fat to protein found in human milk and differing from each other only in dilution; the last two, made up from 7 per cent cream differed essentially from the first three only in a stepped-up protein percentage.

A year later, however, in 1901, Holt's thinking had undergone revolutionary change. He then wrote: "Milk indigestion is not one thing, sometimes it is fat indigestion, in other cases protein indigestion and in still others sugar indigestion. By the modern method of feeding, an attempt is made to separate these conditions and, instead of treating them all in the same way by simply diluting the food and thus reducing the proportions of all the elements, the aim is to reduce only the one that is causing the trouble." By then he must have begun to realize that the high fat percentages were actually bad for some infants and he introduced the new idea of sugar indigestion. However, the most important change in his thought was the concept of specific intolerances to the fat, carbohydrate, and protein of cow's milk feedings, each considered separately. But his faith in the percentage method was perhaps increased by this new attitude because the method furnished the means of juggling the percentages in any way thought desirable to meet the particular pattern required by the infant; the fat could be lowered by using as the basis whole or skimmed milk and the sugar percentage placed anywhere by varying the amount added. In his lectures to us during 1903 to 1905 he several times referred with obvious pride to the percentage method as the "American or scientific method." The problem before the pediatrician had now shifted to finding out what particular combination of percentages the individual infant required; the finding out was by trial and error.

Holt taught us in this period (1903 to 1905) percentage feeding in the greatest detail, and his restrained enthusiasm that could not be missed enveloped the subject with an esoteric aura. Indeed it appeared the very Eden of Pediatries, where skill was most needed and the pediatricians reigned alone and supreme. We students worked hard to master the sesame which opened all doors, particularly as we expected in the final examination one or perhaps two questions.

Evidently by 1905 Holt's suspicions had become aroused that high fat might be dangerous, for he then wrote a paper on the disturbances of digestion resulting from excess of fat in the formula, the common cause for which

was the careless use of Guernsey or Jersey milk. In this article he placed the upper limit for fat in the formula as "3 or 4 per cent." But by 1911 he must have reached the definite conclusion that even 3 per cent fat was hazardous, for in the edition of the booklet of that year the statement occurs that 7 per cent cream is the richest source for modification ever to be used and, two years later, in the 1915 edition, the answer to the question, "Is cream more digestible than milk?" is, "For most infants it is much less so." These statements meant that Holt had now turned his back completely on the full "3-6-1" imitation of human milk. Moreover, in the 1915 edition of the booklet whole milk modifications are pushed up side by side with 7 per cent cream derivatives as standards, coupled with the injunction that 7 per cent cream should be used only if the infant has "robust digestion." It seems odd in view of this warning that Holt should then have advocated even the weaker cream modifications.

In 1916 another great reversal of view is to be noted. In a paper on milk protein digestibility, he wrote: "What are the symptoms of protein indigestion or intolerance? We are compelled to reply that at present we cannot mention any definite symptom or group of symptoms which we can positively attribute to the proteins, in the sense that we can attribute other definite symptoms to the fats and to the carbohydrates." Thus the very premise from which the idea of human milk imitation had sprung was declared false.

Finally, in the 1921 edition of the textbook, in which Howland had been raised to full co-author, and perhaps as a result, the percentage method was definitely dropped, though directions for the calculation of the percentages in whole milk mixtures are provided. Dr. Rustin McIntosh, who served as intern and later chief resident at the Babies Hospital during the years 1922 and 1923, informs us concerning Holt's attitude toward infant feeding during these two final years. "Dr. Holt impressed me with the notion that every infant had a delicate digestion with his own individual tolerance for the separate food components, fat, carbohydrate and protein. In ordering the feeding it was considered prudent to begin with dilute mixtures and then gradually explore the infant's tolerance on a trial and error basis. Orders were written in percentages of fat, carbohydrate and protein, with 'significant' figures given in two or three digits, for example, '2.00-6.00-2.00' . . . under Dr. Holt the evaluation of an infant was incomplete without careful inspection of the stools. In general it was agreed that vomiting meant an excess of fat in the diet, diarrhea reflected an excess of carbohydrate and from the color and appearance of the stools one should be able to tell whether the infant did or did not suffer from protein indigestion." McIntosh cannot recall that any feeding based on cream was used.

During the last years at the Babies Hospital Holt employed Finkelstein's protein milk for diarrhea, regarding it as a therapeutic agent which marked a great step forward. He also experimented with Feer's butter-flour mixture, showing great interest in it and being highly pleased with its use. Evidently Holt was exploring outside the percentage thinking.

In this survey the percentage method appears much less complicated than as

actually presented by Holt to us students, though probably in its most conservative form. The greatest importance was attached to the minutest changes in percentage relationships. No less than fourteen formulas based on 7 per cent cream, in case one chose it as a basis, and fourteen on whole milk, if one started that way, were recommended to be used successively, so that the baby could slide down finally to plain whole milk with never a jar. Rotch of Boston, as stated by Morse, warned against a change in any one of the percentages in the formula in excess of 0.1 per cent.

The percentage method never took root in Germany and Jacobi, a revolutionist socially but conventional adherent of German medicine, continued boldly to champion whole milk formulas. We Holtists used to look on Jacobi with a certain pity as too old to progress. However, Holt's attitude toward the percentage method remained moderate as compared to others, in particular Rotch and his disciples in Boston.*

*In the fourth edition of Rotch's *Pediatrics* (1903) four pages are devoted to equations for the calculation of percentages. The mathematics were perhaps necessitated by the combinations of cream of different strengths and whey, the latter to get rid of the casein. A formidable example is:

$$C = \frac{L(b^1F - a^1P}{ab^1 - a^1b}$$

The rumor was that some Boston devotees carried slide rules. In the *Archives of Pediatrics*, Volume 11, page 488, 1893, appears a photograph of Dr. Rotch with the accompanying legend, ". . . he has done more than any other pediatrist in the world to place the intricate subject of infant feeding on a scientific basis."

Holt records: "Only last month a gentleman called upon me with a new system of calculating precentages, by which he claims to be able to secure with great exactness, and readily, 579 different sets of formulas." Holt's comment was, "Would that the average physician knew how to use intelligently a half dozen." Westcott of Philadelphia developed a "milk modification device for the instantaneous calculation of percentage milk mixtures, which consisted of three revolving disks resembling a wheel of fortune." Dr. Borden Veeder recalls having seen a demonstration of this by Westcott himself. All this shows how deeply percentage feeding had rooted itself in the minds of pediatricians in this country.

It must be remembered that at the time when percentage feeding was developed, artificial infant feeding was in its infancy and groping attempts to find the ideal substitute for human milk were being made on every side. The "percentage movement" was just one of these. As we trace Holt's evolution in regard to it, imitations of human milk were finally abandoned and the primal scapegoat, protein, was exonerated. But Holt seems never to have freed himself completely from the concepts of specific intolerances to fat, carbohydrates, and protein.

Undoubtedly the reason that Holt clung so tenaciously to percentage feeding was that with his great experience and skill he was able to use it with success. In so empirical a subject, experience with a method may be far more important than the method itself. With good supervision, most infants could be reared on cream mixtures. Indeed Morse of Boston, Rotch's successor at Harvard and the last of the old guard of the percentage school, announced his perference for weak cream modifications with their reduced protein content as late as 1935. However, it should be pointed out that percentage differences, and hence the percentage method itself, ceased to have any practical significance so soon as cream was replaced by whole or partly skimmed cow's milk as the basic source, for the resulting modifications then resolved into merely diluted milk plus sugar. Although percentage feeding has now only the importance of a historical curiosity, oddly enough it was actually an important factor in the development of pediatrics as a specialty. Its build-up into a system of great complexity, the feeding difficulties it created, the attitude toward it akin to mysticism, and

finally its grip on pediatric thought, all united to make infant feeding a subject which only the specialist of specialists could tackle.

Before leaving the subject of Holt's teaching of infant feeding it is most important to emphasize that he was a great advocate of maternal nursing. Indeed, he made us students believe it our duty to educate mothers to nurse their babies for at least three if not for nine months. He commented again and again on the lower mortality rates in breast-fed infants and pointed out the great advantages in breast feeding, even if it could be carried on only for the most critical period of the first few weeks.

### HOLT'S PHILOSOPHY OF UPBRINGING

Holt had a philosophy which we doubt if he recognized as such, since it was a part of his nature rather than conscious thought. Its importance lies in the fact that it has dominated pediatric thinking and practice until recently. It can be called the doctrine of environmental conformity. The central idea is that a certain general environmental pattern which is the best for every infant can be formulated: fixed feeding hours of prescribed duration, fixed sleeping habits, fixed dietary, et cetera, and that each infant should be trained from the start, while still vegetative, to conform to it. The method of training is to render the environmental pattern inflexible. The infant finding this resistant, on the one hand, and his needs automatically met by the schedule, on the other, falls in and conforms. An illustration is to be found in the booklet for mothers in the answer to the question, "How is an infant to be managed that cries from temper or to be indulged? Answer: it should simply be allowed to cry it out. A second struggle will be shorter and a third rarely necessary." The opposite extreme, now so much in fashion, namely, to allow the infant himself to set the environmental pattern, is of course a revolt. The Athenians preferred Spartan nurses and Holt's doctrine has a Spartan flavor, natural to his Puritan nature. There is no dispute regarding the ultimate necessity for the individual to adapt to the structure of society, and the method used by society is Holt's—namely, the pattern continues willy-nilly and the individual finds, often by bitter experience, that acceptance pays. Even the followers of the flexible environment school seize every chance to approximate as much orderly routine as the infant accepts. The criticism of the Holt philosophy is its exclusiveness and the rigor of its application. Obviously children are not alike, as the Holt doctrine seems to imply, and the upbringing must vary with the individual. But the Holt formula is the one ultimately arrived at, no matter what the route employed.

### AS A PRACTITIONER

It was Holt's habit to begin the day with a horseback ride in Central Park. He arrived at his office and began work promptly at 8:30. He never said "good morning" to his secretary or she to him, but they fell to work instantly. Each was devoted to the other and there was a perfect understanding.

In 1910 the office was on the ground floor of the family house on West Fifty-fifth Street. The long foyer served as waiting room. Back of this was the office and in the extension was

a smaller room in which were provided the secretary's desk and facilities for doing blood counts and urine analyses. The office looked like a library, with its shelves filled with bound volumes of medical periodicals and its history files. A couch served as examining table and the only visible tools were a desk, scales, measuring device, a stethoscope, and tongue depressor. Holt rarely took notes himself. Usually he and the patient's mother sat by the window, while he personally elicited the history and made the examination. The assistant sat by the desk and made notes as he listened. Later these were typed and filed by the secretary. There were always several toys in the office for the distraction of anxious children. One was a large black crow which flapped its wings when pulled. If necessary to divert the child, Holt would ask his assistant to drag the crow across the floor.

Holt was precise about anything he was doing. While taking a history his questions were to the point and soon led to the underlying facts which often escaped parents. His approach to the child was firm but kind and most children accepted his examination without objection. He treated them like individuals rather than as just problems. He was not always so careful of a parent's feelings. Foolishness or incompetence annoyed him and was likely to bring forth a sharp retort that was devastating. He expected satisfactory work from both himself and those working with him. His perceptions were acute; he sized up a situation in very short order and his conclusions were almost invariably right—family relations and that sort of thing.

Patients came to his office from all over New York City and the country and it is important to emphasize that he kept his fees relatively small. He rarely left New York City for consultations. In the afternoon he did his hospital work, saw some patients in their homes, and did his teaching. He worked on his own medical projects well into the night. During week ends he stayed at his farm in Pleasantville near New York, and spent his summer holidays at his summer camp on Saranac Lake in the Adirondacks, where he played golf and also wrote. In these off periods he devoted himself to his family.

How good a practitioner was he? When one considers how he continually tabulated and analyzed his increasingly large experience, the meticulous care with which he studied his patients and the acuteness of his perceptions and psychological intuition, he probably had no equal in this country at the height of his career. In his later years some of the rising generation, trained in the laboratory and in the newer viewpoints, surpassed him in certain fields of child care, but it is doubtful if even they excelled him in the handling of day-after-day problems.

### HOLT AS AN AUTHOR

Holt's bibliography numbers more than 170 papers and includes three books. We shall first discuss the papers. As a preliminary, however, it is interesting to note that early Holt wrote for the laity; several papers appeared in *Babyhood* and several of his later ones in the *Delineator* and one (1885) in *Kelly's Family Guide!* Scattered among the papers are a half dozen or more addresses.

The first three publications were on topics in adult medicine. Two years after he had begun practice, in 1883, his papers on pediatric subjects begin and continue in a steady succession to the time of his death. In the earlier years they were in the great majority case reports, a few from the Northwestern Dispensary which were necessarily clinical, but most of them combined clinical and gross anatomical studies from the service at the New York Infant Asylum. The way in which the ambitious clinicians of this early period sought to perfect themselves was via the autopsy. The service at the New York Infant Asylum offered a wonderful opportunity for clinical and autopsy correlation, which Holt pressed with all his youthful energy. Actually many contributions of this early period amount to little more than presentations of autopsy specimens, furbished with clinical backgrounds, before the Section of Pathology of the New York Academy of Medicine. At these meetings Holt was a regular attendant and the reports are to be found in the Proceedings of the Section. Evidently this was the time when he was busy collecting and storing experience. It is easy to form a mental picture of the youthful Holt in his private wonderland of the New York Infant Asylum, a Siegfried *im Waldleben,* with sights that were new wherever he turned, himself now turned discoverer and thrilled to report his experiences to others. In 1886 nine papers are recorded and eleven in 1887.

Gradually, presentations of general pediatric topics appeared and these became more frequent as the years passed. Indeed, after 1905, case reports virtually ceased and we begin to find discussions of large subjects; for example, the serum treatment of epidemic meningitis, a report on 1,000 tuberculin tests, et cetera. These more important studies followed the maturation of his experience and they were greatly facilitated by the growth and development of the Babies Hospital. There the increasingly active service provided unusual assortments of cases, the laboratories' contributory data, and the resident staff could be enlisted for compilations and analyses. Beginning in 1903 with the investigation of impure milk feeding in New York City tenement houses, we note the increasing spread of Holt's interest from morbid pediatrics into its neighboring fields of infant mortality, hospitals for children, home versus hospital care, health education, et cetera.

In 1911 appeared the first of a series of biochemical studies. As already recounted, Holt played an important part in the establishment of the Rockefeller Institute and became a member of its Board of Directors of Scientific Research and the permanent secretary of the latter. The appointment to the upper strategic staff of the Institute undoubtedly exerted a profound rebound educational influence on Holt himself, for it brought him, the clinician par excellence, brain to brain with the foremost medical scientists of the day. But his position in the inner circle of the elite paid back in practical benefits as well, in the shape of a grant of funds for studies under his personal direction at the Babies Hospital, and in the provision of expert advisors and guides, the closest of whom were P. A. Levene and Donald van Slyke. The problems which attracted Holt were

biochemical, but he lacked chemical training. Accordingly, he followed the only course possible for him, namely, he employed two experienced chemists, recommended by the Institute, Angelia Courtney and Helen Fales. The twenty-four studies, published jointly from the Institute and the Babies Hospital and bearing the names Holt, Courtney, and Fales, or Holt and Fales, were the result. The subjects chosen by Holt were evidently those which had troubled him particularly in infant feeding—composition of casein curds, effects of high protein diet, losses in diarrheal versus normal stools, and the absorption under varying conditions of calcium and of fat. As the studies proceeded, their value came to consist more and more in the establishment of norms. The very last studies, outside biochemistry entirely, were the determination of the total caloric requirements and optimal distribution of calories between protein, fat, and carbohydrate in the diets of healthy older children. These were arrived at empirically by analyses of the diets actually taken.

Interestingly, these papers demonstrate how scrupulously Holt carried out his original resolve to center on pediatrics while required to practice general medicine—only the first three had to do with adults. They also show more important things. Emerging from the turmoil of practice, teaching, and other occupations and responsibilities, they disclose an exceptional industry, enterprise, and ambition to add to knowledge. They demonstrate likewise a most unusual freshness and alertness to medical progress and an ability to change with the latter and to seize on new things. In the succession of titles one can perceive familiar milestones, intubation, diphtheria antitoxin, sanitary milk production, the von Pirquet test, the bacteriology of respiratory disease, the Wassermann reaction, salvarsan, the Fredet-Rammstedt operation, the vitamins, and finally the biochemistry of nutrition. Another noteworthy feature is that the papers cover a wide range of subjects, indeed along all phases of child health. We cannot think of any other pediatrician whose interests have been so wide and so evenly distributed. Considering the papers as a whole one cannot help being impressed with the undercurrent of sound judgment and shrewd common sense running through them.

The papers are all factual or concerned with practical ends and are free from speculation and hypothesis. One gains the impression that theory did not appeal to Holt, but rather that his natural zest was for gathering of the materials of knowledge and their coordination, simplification and uses. The papers are written in short, crisp, clear sentences, proceeding directly to their objectives and never deviating. The same holds true for the addresses, some of which contain striking sentences: "If today we have a broader vision of our science than the men of 25 years ago, it is not because our sight is better but because we stand on their shoulders."

An additional word must be said about the biochemical studies, since they mark a great transition in Holt's development, namely, from the morphological into the physiological field. They were mostly balance experiments, new in this country, though familiar enough in Germany. No micromethods then existed and new ways and adaptations had to be developed for which achievements Holt's assistants deserve

great credit. The studies were most laborious and painstakingly executed. The reports of them are accompanied by thorough reviews of the literature and show that Holt had acquired a mastery of each subject under consideration and that he saw clearly the significance and relation of the results obtained. One can say of these biochemical investigations that they were thoughtful, scholarly performances and that, if reported for the first time today in modern chemical terminology, they would be regarded as important contributions to basic knowledge.

One in particular stands out, "The Chemical Composition of Diarrheal as Compared to Normal Stools in Infants"* because it indicated prophetically a path of future development, one not adequately explored until recently.

"Normally, 40 per cent of the ash intake is lost in the stools; this is chiefly calcium phosphate, of which cow's milk has so great an excess. In very loose diarrheal stools there is lost 84.3 per cent of the intake. The proportion of calcium phosphate shows but a moderate increase over that in normal stools, 79 as compared with 67.2 per cent of the intake. The great increase in the total is made up of the other salts. The magnesium loss is 100 per cent, indicating that it very slowly enters into combinations in which it can be absorbed. The loss of calcium and magnesium occurs almost exclusively in the stools, only traces being found in the urine. Of the remaining elements, the loss in the urine must be considered in estimating the balances. Chlorine, potassium and sodium are normally present in the stools in relatively small amounts, but in the urine in large amounts. In diarrheal stools we find an enormous increase in the quantity present in the stools and a corresponding reduction in the amount eliminated by the urine. But the increase in the stools is so great as to create a negative balance of 10.3 per cent in potassium and 8.7 per cent in sodium. This indicates the loss from the body itself.

"The ratio of the loss of salts to the intake is one of the most striking characteristics of loose, diarrheal stools and furnishes an important suggestion as to treatment. In attempting to supply this loss by hypodermoclysis it should be remembered that not only are water and sodium needed, but potassium and magnesium as well. With these facts in mind a better solution for use in hypodermoclysis can certainly be devised than a normal saline or than Ringer's solution."

The above is the only instance we are aware of in which Holt speculated and it makes us wish he had indulged often. One cannot help but believe that, were Holt alive and in full vigor now, he would be at the very forefront of biochemical physiology and pathology. If micromethods had been available, he would probably have extended his investigations to the blood. As it was, he was close to the realization of diarrheal acidosis, since his balance studies furnished a basis for it, and he was prevented from developing a replacement fluid containing potassium by lack of the data concerning the status in the blood necessary in order to proceed.

Most of the papers are now lost sight of in the pile of medical knowledge, having made their contribution to it. But a few still stand, for example, "Tuberculosis Acquired Through Ritual Circumcision," a collection of forty or more cases; "Hypertrophic Stenosis of the Pylorus in Infants," recording instances of persistence of the tumor; "Infant Mortality—Ancient and Modern," a most scholarly address which must have required extensive reading. The studies on calcium and fat retention have a

*Holt, L. E. Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. 9: 213, 1915.

present-day as well as historic interest. The papers on the caloric requirements of older children, which resulted in the "Holt-Fales standards," have probably the most immediate practical importance of all.

Holt termed his booklet for mothers, *The Care and Feeding of Children*, a catechism; he might have called it a Vade Mecum, for that is what it at once became. A catechism is a summary of principles in the form of questions and answers; it is all inclusive, rigid, factual, precise, definite, authoritative, free from speculation, admitting no doubt. Holt's booklet was all this. If one wishes to know Holt's mind, he finds it mirrored in the booklet. Each question is aimed at a single point and one question follows another in perfect sequence. The answers have the exactness and brevity of definitions. Every contingency is covered—a convulsion! The mother rushes to the book. What to do is all there in one, two, three order—till the doctor arrives. "Are there valid objections to kissing? What are the most common bad habits of young children? Answer—sucking, nail biting, dirt eating, bed wetting, masturbation." Tennyson recognized in his "In Memoriam" that the cry of the infant had meaning, when he wrote, "And with no language but a cry." Under the topic, "Cry," Holt lists six varieties—"normal," "pain," "hunger," "temper," "illness," "indulgence or habit" and informs the mother how to tell them apart! That page must have been thumb-worn. The list of foods tabooed is like the catalog of the unclean beasts in Leviticus. The booklet, now outgrown, written innocently for a local need, is a masterpiece of clear incisive exposition, a little gem full of sparkling facets. It was most original and far in advance of its time, setting an innovation which has bred many descendants. As a sidelight, the Grolier Club of America* in 1946 selected and published a list of 100 books "which influenced the life and culture of the American people." In company with such representative selections as Benjamin Franklin's *Almanac*, Longfellow's *Ballads*, *Uncle Tom's Cabin*, Hawthorne's *Scarlet Letter*, Whitman's *Leaves of Grass*, appears Holt's *The Care and Feeding of Children*. Its importance in the development of pediatrics in this country will be referred to later.

Before leaving the subject of the booklet it is only fair to point out that in recent years some pediatricians have felt that through the projection of its rigid philosophy of upbringing the booklet had had a harmful influence.

The famous textbook, *The Diseases of Infancy and Childhood*, was also a model of clear concise exposition. As students we used to find it dull reading like a compendium *in extenso*, in contrast to Osler's textbook which was enlivened by his vividness of style and allusions here and there to history and literature. Osler managed to inject himself into his writing but Holt seemed to strive for objectivity, the logical orderly presentation of facts in their bareness. Actually, Holt's writing was to a marked degree personal experience, but it was his nature that everything not essential be scrupulously sacrificed for crystal clearness and condensation. "Holt" was essentially a manual for medical students,

*New York Times* Book Review, *Books That Influenced America*, vol. 51, p. 7, 1946, David A. Randall.

though on the shelves of every general practitioner in the country. The descriptions of disease were in conventional patterns, the clinical picture a composite of statistical averages. When stuck with some rare disease or unusual manifestation, we young doctors did not get much help from "Holt." But the work was a monument, and its importance can scarcely be overestimated. It lifted child illness and care out of chaos and defined and coordinated it and brought it all together as Pediatrics. At the same time it separated pediatrics from internal medicine and placed it on a high plane of excellence. In concise form it furnished for the first time in any language a clear, well-balanced, complete exposition of the child in health and disease and of the principles of care. The result was to make pediatrics in this country a definite entity which gave ample room for a life's work and fully justified specialization. As presented by Holt, pediatrics offered two major opportunities: one, infant feeding; the other, the infectious diseases. It is interesting that now the pediatrician has lost his monopolistic rights in both, in the former because his pretentions were unsound, in the latter because science has furnished new easy methods of attack open to all.

### AS A MAN

We now add to the portrait, as drawn thus far, some final touches of a highly personal and intimate kind, hoping that they may impart to it reality and life.

Holt showed economy of words. His approach was direct, to the point, incisive and often blunt. When an intern at the New York Foundling Asylum, I (E. A. P.) was enthused to raise money for a milk laboratory and asked Dr. Holt for an appointment. He gave me one at his office at 8:30 the following morning. When I explained what I wanted he said in three or four sentences that the institution was badly conducted medically, that he would not assist me, and that he advised me to drop the project.

Dr. Rustin McIntosh gives an amusing example of Holt's terseness and inflexibility on what was to him (Holt) a moral issue.

> About 1900 my sister, then a young girl, had digestive trouble which baffled the local practitioners in Omaha. (In retrospect, I surmise that she had a mild grade of coeliac disease.) She was brought, in desperation, all the way to New York to see Dr. Holt. Therapy took the form of a regulated way of life, including a strict diet which avoided sugar and most forms of starch. The symptomatic response was so gratifying as to demonstrate clearly that Dr. Holt knew what he was dealing with. After some weeks and months of encouraging improvement my sister was so greatly changed from her former state that my mother, looking ahead, was emboldened to write to Dr. Holt to ask his sanction for a special Christmas celebration, a departure from the strict diet to the extent of permission for one (1) piece of candy. I'm sure that my mother looked on this one anticipated treat as a symbol of Peace on Earth, Good Will Toward Men.
>
> The reply, written in Dr. Holt's hand, has alas not been preserved, but was said to have run as follows:
>
> "My dear Mrs. McIntosh:
>
> Why you should wish to make your daughter ill on Christmas rather than on any other day I fail to understand.
>
> Yours faithfully,
> L. Emmett Holt."

It was characteristic of Holt not to praise. When he engaged his secretary, he told her that he would never praise her but would tell her if her work was unsatisfactory. She informs

us that during her many years of service he never once said to her "a single unkind word." When she made an error, she would realize that he knew, but he never referred to it.

Howland used to describe the incident when Holt came nearest to praising him. Holt had seen a sick girl at her home in the morning and asked Howland to drop in to see her that afternoon. Howland discovered appendicitis with abscess. He telephoned Dr. Holt, who came immediately and confirmed the diagnosis. As they were walking down the steps to the street, Holt turned to Howland remarking, "Well, Doctor, it pays to keep your eyes open."

At the Foundling Asylum, Dr. Holt asked Dr. George Smith, the resident, to tabulate the gross autopsy findings in children having died of tuberculosis. Smith started immediately and sat up working the entire night. By noon the following day he had completed his tabulation. When Holt arrived for rounds, Smith came forward with evident pride, saying, "Dr. Holt, I have your tabulation ready." Holt took it from Smith and, putting it in the inside pocket of his coat without looking at it, remarked, "Thank you, Doctor." Smith was crestfallen but never talked about it.

One could not help wondering what it was in Holt which evoked such efforts to win from him praise or sign of favor. The reason could not have been solely his importance. A factor certainly lay in the tantalizing conundrum of his reticence. The adulatory efforts to please were on occasions painful to witness.

Holt was always matter of fact. When the Harriet Lane was dedicated in 1912, Dr. Holt was invited to make the address of the occasion. Dr. Howland delegated me (E. A. P.) to show him round the new Harriet Lane. I recall that Holt asked just two questions, "Doctor, what is the composition of the mattresses?" and "Doctor, how many cubic feet of air space per patient in the wards?" I was reminded of Conan Doyle's story about Brigadier Gerard. The Brigadier was ushered into Wellington's presence in all the exhilaration and excitement of the French temperament at the prospect of meeting the great man. All Wellington said was, "What weight do you put on your mules, Sir, in the French service?"

It was through my classmate, Frederic Bartlett, that I (E. A. P.) chanced to substitute at the Babies Hospital at the end of my second year. The Director of the Hospital was a remarkably fine woman, Miss Wheeler. Dorothy Reed, who described the "Dorothy Reed cell" in Hodgkin's disease, and a pet of Dr. Osler, was resident, and the distinguished Martha Wollstein was pathologist. I recall that before beginning our substitution Dr. Holt called us to his office and gave us a private lecture on how to get along with women. He ended by telling us that we could use the elevator going up but must always walk down. A few years later he changed his house staff to men.

Holt had a sense of humor which probably missed nothing but any internal ebullition seldom found expression, and then only, as his secretary remarks, "in a twinkle of the eyes." He had wit, too, but with the quality of crisp parchment crackle. One day the door flew open and a mother came in half dragging a child who was screaming and kicking vigorously. Dr.

Holt was standing to one side and I (H. H. M.) in the corner. When she reached the middle of the office, she cuffed the child and then dropped her. The child lay on the floor wiggling, squirming, and screaming at the top of her voice. The mother looked at Dr. Holt, who was standing there, and it was easy to see that the mother was frantic. She said, "I do not know what to do with her, Dr. Holt. I spank her every day." Dr. Holt deliberately put on his pince-nez, looked down at the child squirming on the floor for several seconds that seemed like minutes, and then looked at the mother, saying, "I have found that to be of much help, spanking needs to be in the nature of a treat." The mother looked flabbergasted. I always felt that she got the value of the price of admission with this one remark, if she had the sense to recognize it.

Holt could pun. Rustin McIntosh relates that when Dr. Holt had finished examining a child brought in by a young doctor with a diagnosis of appendicitis, he observed, "Doctor, the trouble is not with the Appendix; it is with the Table of Contents." At a meeting of the American Pediatric Society, Dr. Kerley reported experiences at some length. When he had finished, Holt asked him if he had tried yeast. Dr. Kerley, evidently perplexed, replied that yeast had not occurred to him, whereupon Dr. Holt remarked, "I wanted to get a rise out of Dr. Kerley."

We have referred to Holt's rare psychological insight. Rustin McIntosh supplies an interesting illustration. Dr. Holt was busily engaged writing at his desk at the Babies Hospital when a small boy came by and said, "Hello." Dr. Holt stopped, looked at the boy, answered, "Hello," and then resumed his writing. After a few minutes, he turned to McIntosh, "Doctor, the best way to make friends with a child is not to try."

Howland used often to talk about Holt. He would say, "His mind is as smart as a steel trap." Howland never applied this phrase to anyone else and I (E. A. P.) used to wonder why he invariably selected it for Holt. It would have been inappropriate for a poet or a thinker; it could fit only some kind of man of action. A steel trap does not wander in search of its object; it sits in the line of traffic, waiting for whatever comes its way; its spring is automatic, instantaneous, and marked by a clash and its grip fast. The figure fits all along.

In this connection Alfred Hess once observed, by way of comparing Holt and Jacobi, that Holt would not be likely to recognize a new disease. Holt's mind was neither highly imaginative nor was it profound in the scholar's sense; it was an intensely practical mind, c o n c e r n i n g itself largely with knowledge which offered promise of application to the problems of known or foreseeable experience—the mind, primarily, of a doer. In a letter to his son about to work at the Harriet Lane Home he wrote, "I hope you will not lose interest in the clinical side of pediatrics, for it is only its practical application which justifies research, according to my way of thinking." He was by nature conservative, loathe to venture into uncharted seas. Yet once his mind had grasped the concept of a new disease, it was unlikely thereafter to escape him.

Howland repeatedly said that Holt's deed was better than his word. One

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cannot but wonder if this trait, which all realized, may not have been intensified because his emotions were so restrained. A contract to him was sacred.

Howland again and again affirmed that Holt retained an open mind, one always capable of conviction. Holt's evolution medically, already noted, bears this out. In the early 1900's, when we were his students, he assumed that practice was the sole goal. When the "full-time" movement was started, he was doubtful about its correctness but finally accepted it fully. Once he inquired of Howland whether he, Holt, was himself too old to enter the laboratory.

Howland also used to say that in his opinion, Holt was a greater man than Osler. Of course the only justification for bringing the two together is that each towered at the pinnacle of his branch of medicine in the United States and each was the author of a classic textbook. Osler was a humanist, essayist, historical scholar, intensely gregarious, outgoing, and warm. Holt was a man of execution. As just indicated, Howland's admiration for Holt and his devotion were unbounded; his attitude was filial. Holt's influence was repeatedly demonstrated in the Harriet Lane: Howland's feeding methods were half Czerny, half Holt (not the percentage method), his informal clinics copies of Holt's, and in his handling of private patients one could see Holt's ways. Holt, in his turn, reciprocated fully, admiring, perhaps a bit enviously, Howland's sparkling brilliance and enterprise and, as he grew older, leaning on Howland more and more heavily for information and guidance, as new regions in medicine, denied to him but familiar ground to his younger friend, continued to open. So far as he was able, he threw on Howland his mantle.

Dishonesty, Holt's Puritan mind could not stand, particularly in a physician. When a prominent Boston pediatrician published bodily long passages from an article by Howland and Marriott as if coming from his own mind, Holt sent to him copies of the two, typed in parallel, with the laconic message, "What is your explanation of this?"

Holt's power over people was remarkable. One of the prime movers in transferring the New York Academy of Medicine from Forty-third to 103rd Street, he was particularly interested in raising funds for the new building. Dr. N., a prominent pediatrician in New York City and one of Holt's assistants at the Babies Hospital, confided rather ruefully that Dr. Holt had assigned him a contribution of $400.00.

In New York City, save for a compact coterie at Cornell Medical School where Joseph Winters was professor, and in American Pediatric Society circles generally Holt enjoyed dictatorial power. His advice was invariably sought when a pediatric vacancy was to be filled. He could make any appointment that he wished anywhere. When Dr. Linnaeus Le Fétra resigned the pediatric service at Bellevue Hospital, Howland was exceedingly anxious to receive it, as it was the best in New York City. Howland used to discuss his chances with me (E. A. P.) each morning on rounds at the New York Foundling Asylum, one morning in elation, the next in despair. At the end of three weeks, when he had given up hope, Holt suddenly informed him that he was appointed.

Dr. Borden Veeder, in his reminiscences concerning the 1910 meeting of the American Pediatric Society, recalled:

A Case Report of a "Cured Case of Tuberculous Meningitis" had been presented by the professor of pediatrics in a medical school in the East. The child had developed symptoms of meningitis with an increased lymphocyte count in the spinal fluid. Instead of progressing to the usual death, the symptoms gradually cleared and complete recovery took place. No organisms were found in or were cultured from the fluid. When it came to "New Business," Dr. Holt, who as usual was sitting in the front row, stood up and was recognized by Dr. Morse, the president. "Mr. President, I move that the paper presented by Dr. X on a cured case of tuberculous meningitis be expunged from the records of the Society." It was immediately seconded by someone and then a painful awkward period followed in which Dr. X tried to say something but was obviously totally bewildered. The motion was apparently carried as the paper does not appear on the records of that meeting.

What was the secret of the power over people possessed by this small, quiet-spoken man? The power was of course in his total personality. He was slow to be convinced, but moral conviction and action lay very close and, when action came, it was with all the force of certitude. His approach was simple, clear, direct, brief. If facts were involved, he had thought them out. His appeal was to reason, not the emotions. His judgment kept him from the doubtful or impractical. He acquired the twofold moral ascendance which goes with believing one is right and in being believed to be right. He remained detached. An additional factor was his psychological insight. He knew instinctively those with whom he dealt, whether patient, member of a hospital board, a possible philanthropist, or an assistant. It might be added that he did not reveal himself.

Did this man have heart-to-heart friends? Certainly he had some as a young man. All that we writers know is that between him and even his closest assistants there always remained an impenetrable barrier. Howland and Holt, closest in their relations, never used their first names. Bartlett,* who had tutored the Holt children, came closest to breaking through. The opposite of Holt in all particulars, almost parading disorder in his appearance, impulsive, uninhibited, unexpected even to himself, trusting always to intuition, he acquired the license of a court jester. Holt was fond of Bartlett, enjoyed his free and easy attitude and was amused by his ebullient spontaneity. At least on one occasion Holt broke through the barrier from his side with, "Bartlett, here is fifty cents. It is time to get your hair cut."

The letters to his immediate family are of great importance, for in them the veil is completely lifted and the inner nature of the man revealed. His letters are outgoing, even gossipy, recounting the happenings of the day and full of expressions of endearment and solicitude. To his wife: "As I stood by his bedside this morning and saw Eliza with her heart almost bursting with grief, I realized as never before how inexpressibly dear you are to me. . . ." (Eliza was Dr. Holt's sister. Her husband was dying.) His letters to his children show that he followed closely their activities and interests and exhibited constant concern over their development. The form which this latter takes throws much light on his character. Not in a single instance is there a sign on his part of

*A most amusing and not too exaggerated account of Bartlett will be found as a Profile in *The New Yorker* of July 15, 1944, page 20.

any ambition for them for what is ordinarily grouped under the hackneyed expression of "worldly success." On the contrary it was that they might always be governed by the highest standards of conduct and be "captains of (their) souls." "We all ought to look at life as a great opportunity—the one and only chance we will have of making the very best and most of ourselves. It is not simply fame or fortune that we should aim at, but at the satisfaction which comes and comes only from *something which is worth while really done well.* It may perhaps not make such a great difference exactly what the thing we finally decide to do is, provided it is doing something that the world needs to have done." And again, "To achieve mastery over ourselves is really the most important thing to have gained in life, and when this is once done, all other conquests by comparison are easy," and, referring to himself, "Well, some queer things have come to me in life; these things don't please my vanity. I think they rather make me feel humble and quite undeserving." In his last letter, written from China a few days before his death, "There is nothing in the world so nice as friends, and especially when your relatives are also your dear friends, but most of all your children." Though a regular church goer and supporter, the satisfactions of his religion were evidently of this world. The letters disclose the real man as simple, domestic, affectionate, with the highest values in life completely undisturbed by his successes. They unfold a lovely character. It is a pity that the outside world could not have looked in and known him as he really was.

## INFLUENCE ON PEDIATRICS

Under Holt the Babies Hospital continued, as it was created, a one-man institution. All power was in his hands. Extremely able young men passed through the service and in doing so received the imprint of his personality and some later rose to great eminence in the outside pediatric world. But promising young men were not retained and promoted and the senior attending staff, recruited from New York City practicing pediatricians, really did no more than try to carry out what they regarded as Holt's ideas and wishes. Holt never developed a University Clinic in the sense of today. His conception seemed not to extend beyond the training of his young men for practice and that was the attitude of the time. Osler did not establish one, although he took the first step, for he did surround himself with a nucleus of able clinicians whom he had raised, so to speak, and who divided with him clinical and teaching responsibilities. The University Clinic in its present-day sense originated only with the establishment of the "full-time" movement at Johns Hopkins in 1913. Holt's influence, like Osler's, was imparted not through pupils but rather directly to the outside world.

Although Holt was an international celebrity, his influence on pediatrics was confined to this country and Canada, except perhaps for some overflow into other English-speaking countries. Early in his professional life he acquired a reading fluency in French and German medical literature and the references in his papers, including some of the earlier ones, show a familiarity with both. However, we do not recall that on a single occasion he

brought continental viewpoints into his teaching. Certainly his textbook gives no evidence of foreign influence, this in contrast to Rotch's *Pediatrics* which abounded with references to foreign literature. One can say with truth that Holt spent his professional life assiduously gathering personal experience, sorting it out, and tabulating it in statistical analyses, of which he was very fond, and systematically enlisting his assistants and associates to work on them with him. His own development as a pediatrician was peculiarly *sui generis*. As the result of his natural growth, he remained uninfluenced by the confining, conventional habits of thought in medicine which surrounded him and remained able to see the problem of the child realistically, exactly as it was, not in a one-sided but in an all-round perspective. Thus in his thinking it was as much the function of the pediatrician to aid the child to grow up healthy, physically, mentally, and morally as it was to care for him when sick. In creating this conception of the bilateral function of the pediatrician, the booklet had great influence. That it chanced to be the precursor of the textbook is important, for it educated the laity to expect from the child's physician supervision in all aspects of upbringing. This clear-cut inclusion of preventive medicine in the responsibility of the physician was so far in advance of its time that adult medicine is only now beginning to arrive at it.

So, when Holt, chiefly through the channels of his two books, shaped pediatrics in this country, the form fitted so perfectly into a general need that pediatrics has flourished here and pediatricians have multiplied to an extent which is unique. In Great Britain pediatrics never emerged from general medicine until the National Health Service made it an entity; in France preventive pediatrics early acquired great importance but remained detached in the hands of special groups. In Germany it has kept in much the same confinement as general medicine. The great numbers of pediatricians, scattered over this country, even in small centers, acting as experts in all matters pertaining to the child, directing and educating at welfare clinics, and teaching hygiene and preventive medicine in the home, while meeting the problems of illness, are all the outgrowths of the pattern which Holt gave to pediatrics when he launched it on its way. We have said that Holt was "a born teacher" and although he was a great physician and undoubtedly the foremost and most progressive student in pediatrics of his time in this country and a power in all aspects of child welfare, his claim to fame is as a teacher, and the country was his classroom. Embued with a sense of mission, at heart a reformer, his teaching was to him a gospel, taking the form of the betterment of child care, and with the power of a gospel his influence spread into every home. If a great pioneer in pediatrics in this country, he became also such in public health when he made preventive medicine a full half of pediatrics. More than any other single person in this country he laid the groundwork for "the age of the child." American Pediatrics is Holt's monument.

*Edwards A. Park*
*Howard H. Mason*

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# Comments on Current Literature

## ENCEPHALITIS LETHARGICA, TYPE A ENCEPHALITIS, VON ECONOMO'S DISEASE

VON ECONOMO'S disease is a meningoencephalomyelitis characterized by a wide variety of signs and symptoms in different individuals, and in the same patient at different stages of the malady. Knowledge of this disease dates from von Economo's report of a small outbreak in Vienna during the winter of 1916-1917. Following closely upon the description of this so-called "lethargie" type of encephalitis, reports of similar experiences in other countries appeared until it became evident that this clinical entity was present in nearly all parts of the world. In 1924 an epidemic occurred in England and Wales which involved 5,039 cases.[1] By the beginning of the next decade, however, confirmed cases of this disease had become sporadic, and by 1939 the disease was considered rare. Since it had occurred in close relationship to the pandemic of influenza in 1917-1918, many observers attempted to connect the two diseases etiologically. If such interrelation actually exists, it remains to be demonstrated, the present conception being that they are due to entirely separate etiological factors.

Although the exact etiology of lethargic encephalitis is not known, its general aspects conform to those of a virus infection. A strain of herpes simplex has been suggested as the possible etiological agent; this suggestion has not been substantiated, however, by the pathologic findings or by clear-cut laboratory studies, and the disease has not been reproduced in experimental animals. Having a definite seasonal incidence, occurring chiefly in the winter and early spring months, its spread is probably not dependent upon arthropod vectors. The manner of spread among human subjects is not understood; contact or droplet infection and carrier states have been suggested as of possible importance in the epidemiology. In recent years the disease has been sporadic in distribution, and when present in a community seldom affects a large number of persons at the same time. Individuals of all ages are susceptible, cases being described in young infants and in the elderly. While the most susceptible period seems to be the third and fourth decades of life, the condition does occur in children; 25 per cent of the cases described have been in persons from 10 to 20 years of age. The incidence is slightly higher in males than in females. The occurrence of more than one case in a given family is unusual. The incubation period is thought to be extremely variable, from a few days to a month or longer, with the suggested average of about ten to fourteen days.

While this disease was prevalent in North America and Europe for a period of about ten years (1916 to 1925), no epidemic outbreaks have been reported in recent years. A few sporadic cases, however, continue to be reported, the patients progressing slowly to maximal disability; of three cases[2] described in 1951 two became to all appearances moribund, and remained at this low ebb for a period of about two weeks, improving very slowly to total neurological recovery. One in whom the acute manifestations were mild, passed through a stage similar to parkinsonism. In one series (1954) seventeen patients[3] suffering from a mild acute illness with typical manifestations and sequelae are described, raising the question as to whether a mild form of von Economo's disease exists.

In the *British Medical Journal* for May 19, 1956, three of these sporadic cases are reported by Espir and Spalding,[4] indicating, as the authors point out, "that this disease still occurs and that postencephalitic Parkinsonism may be due to recent infection." Two of these patients, aged 19 and 28 years, were military personnel stationed in the same general area in Northern Germany, and one was a cadet, 16 years of age, stationed in England. In all three instances the signs and symptoms during the acute phase were typically those associated with encephalitis lethargica. In two of the cases the acute illness merged into a chronic postencephalitic state with parkinsonism. In the case of the 16-year-old cadet recovery was slow but appeared to be complete, and in five months the patient returned to full activity. Electroencephalographic tracings which had been obtained on the second day of hospitalization (about the fifth day of illness) showed evidence of generalized disturbance, but no localized or focal abnormalities; electroencephalograms taken four and eight weeks after onset showed general return to normal, in keeping with the clinical improvement. Three years later, however, this boy began to show signs of postencephalitic parkinsonism associated with characteristic behavior disturbances. These included episodes of disorientation, tremors, cogwheel rigidity of the upper limbs, transitory speech impairment, and spasmodic conjugate deviation of the eyes upward, in a manner suggestive of oculogyric crisis. Behavior disturbances were marked, including a series of crimes, mainly violent and apparently unpremeditated, with little attempt to avoid detection. Close surveillance became necessary.

Early diagnosis in von Economo's disease is usually difficult. There are no laboratory tests available at present for specific diagnosis. Spinal fluid findings are variable; cell count is usually low, in 45 per cent of the recorded cases, less than ten cells per milliliter. In a relatively small number of cases, spinal fluid pleocytosis was moderate (100 to 300 cells), with a preponderance of mononuclear cells. Pressure and globulin content may be elevated. Certain diagnostic points have been considered significant: signs suggesting involvement of the mesencephalon and the cranial nerve nuclei; ophthalmoplegia; variable signs and symptoms suggestive of a widespread "patchy" distribution of lesions in the central nervous system. The masklike appearance of the face which develops in the course of the illness has been considered a highly characteristic feature. In some instances only prolonged observation makes the diagnosis possible.

Since tuberculous meningitis is especially common in children, differentiation from this disease is of importance. The onset and early symptoms may be quite similar in the two diseases. Poliomyelitis may simulate von Economo's disease, particularly the bulbar type in which disturbances of speech and deglutition occur, plus involvement of the cranial nerves.[5] Meningeal symptoms may predominate in the early stages of poliomyelitis. Important differential points are early rigidity of the spine in poliomyelitis[6] and the usual localization of the lesions in the spinal cord, rather than in the brain stem. In poliomyelitis, somnolence is relatively rare and is less persistent than in encephalitis lethargica, and in poliomyelitis the sensorium is usually clear. In rapidly fatal cases, however, it may be impossible to differentiate the two diseases clinically.

In two of the cases of von Economo's disease reported recently by Espir and Spalding[4] attempts were made to isolate a viral agent from body fluids (blood and spinal fluid) and from stool specimens, but without success. Antibody studies involving three neurotropic strains of virus, in addition to strains of poliomyelitis, gave negative results. The authors point out that until some clarification of the etiology of this disease is possible, the diagnosis remains a clinical one. A number of observers has emphasized

the chronic aspects of von Economo's disease, postulating that some infectious agent may remain latent for a relatively long period, and then regain activity, invading more tissues, and initiating a progressive pattern of symptoms entirely different from that which characterized the onset of the infection.

There is no specific treatment for encephalitis lethargica in the acute stages. The use of convalescent serum from a patient who has recovered from the disease is not to be recommended, since exact etiological diagnosis is not possible, and since the effectiveness of such serum is doubtful, once the central nervous system changes are apparent. Nursing care, maintenance of general hygiene, nutritional status, and hydration are extremely important, especially during the acute phase or during somnolent phases. Sedation may be of value in selected cases.

The sequelae which occur at varying intervals following the acute phase merit therapeutic consideration. In children especially, and in young adults, bizarre forms of parkinsonism are observed: torticollis, torsion spasms, myoclonus, oculogyric crises, facial and respiratory ties, and peculiar postures and gaits.[7] Other sequelae seen more commonly in children than in adults include behavior disorders and emotional instability, usually with no evidence of intellectual impairment. A broad therapeutic program embraces physiotherapy, psychotherapy, and the selective use of drugs. Hyoscine and stramonium, antispasmodic drugs, which have been available for many years, are still of value in patients with long-standing postencephalitic symptoms. The newer antispasmodic drugs such as Artane, Pagitane, Cogentin, Kemadrin, and Parisdol have been favored in recent years.[4, 8] Artane, particularly, is tolerated well, and has been found beneficial to most patients. In a recent study of parkinsonism by Schwab and Chafetz,[9] eighty-seven patients were followed for periods of from three to twenty months; 52 per cent responded favorably to Kemadrin with good symptomatic relief. Kemadrin was employed to good advantage in some instances in combination with atropine-like drugs. A comparison of Kemadrin with Artane showed Kemadrin somewhat more effective in the series of patients studied by Schwab and Chafetz.[9]

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# News and Notes

The following were certified by the **American Board of Pediatrics,** at the examination at Cincinnati, Ohio, June 8, 9, and 10, 1956.

Dr. Carol Remmer Angle, 418 S. 82nd St., Omaha 3, Neb.

Dr. Harry Daniel Baernstein, Jr., 810 Main St., Racine, Wis.

Dr. Bert Ira Beverly, Jr., 715 Lake St., Oak Park, Ill.

Dr. James F. Boysen, 650 Orpheum Bldg., Sioux City, Iowa

Dr. Audrey Kathleen Brown, 264 Alter Rd., Detroit 15, Mich.

Dr. Donald F. B. Char, 206 E. Penn St., Philadelphia 44, Pa.

Dr. William Rogers Chattin, 4209 Roselawn Dr., Indianapolis, Ind.

Dr. Louis E. Cimino, 2702 Comanche Dr., Amarillo, Texas.

Dr. Wilfred Qualls Cole, Jr., 2912 N. State St., Jackson, Miss.

Dr. Robert Frank Cooper, 2998 Sullivant Ave., Columbus 4, Ohio.

Dr. Keith M. Coverdale, 1167 Laurel Ave., Bowling Green, Ky.

Dr. Dorothy Gildea Cunnick, 519 Davenport Bank Bldg., Davenport, Iowa.

Dr. Anton John DeFede, 2441 "G" St., Bakersfield, Calif.

Dr. David G. Dickinson, University Hospital, Ann Arbor, Mich.

Dr. Mark S. Dine, 8600 Winton Rd., Cincinnati 31, Ohio.

Dr. Paul Joseph Dunn, 212 Linden Ave., Oak Park, Ill.

Dr. Violet Friedman, 284 Eastern Parkway, Brooklyn, N. Y.

Dr. Max J. Garber, 23603 Farmington Rd., Farmington, Mich.

Dr. Albert Goldman, 4616 N. Western Ave., Chicago 25, Ill.

Dr. John E. Gustafson, 724 21st St., West Des Moines, Iowa.

Dr. Gunyon Mitchell Harrison, Southwestern Polio & Respiratory Center, Houston 3, Texas.

Dr. Alexis F. Hartmann, Jr., 7433 Teasdale Ave., St. Louis 5, Mo.

Dr. Emmett M. Heiligman, 1237 E. Main St., Alhambra, Calif.

Dr. George W. Herring, 715 Arledge Rd., Hattiesburg, Miss.

Dr. Louis Fillmore Heyman, 19483 St. Mary's, Detroit, Mich.

Dr. Don M. Hosier, 695 Bryden Rd., Columbus, Ohio.

Dr. Robert Corlett Howard, 1750 E. 19th Ave., Denver, Colo.

Dr. Donald W. Jackson, 631 S. Eremland Dr., Covina, Calif.

Dr. John Alexander James, Southwestern Medical School, University of Texas, Dallas, Texas.

Dr. Forest Davenport Jones, 104 Ponce de Leon Ave., N. E., Atlanta, Ga.

Dr. John Theodore Jones, 134 S. St. Clair St., Painesville, Ohio.

Dr. Thad H. Joos, 979 Vernier Rd., Grosse Pointe Woods, Mich.

Dr. Marita Dolores Kenna, 4740 Liberty Ave., Pittsburgh 24, Pa.

Dr. Leo Stanley Konieczny, 515 Park Ave., Ironton, Ohio.

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Dr. Kathryn D. Lavrich, 1979 Connecticut Ave., Cincinnati 24, Ohio.

Dr. Walter Xavier Lehmann, Post Office Sq., Wilton, Conn.

Dr. Ray B. Lewis, 112 Parkhill, Columbia, Mo.

Dr. Elizabeth Jean McGavran, Whitesburg Memorial Hospital, Whitesburg, Ky.

Dr. Jack D. MacDonald, 1125 Offnere St., Portsmouth, Ohio.

Dr. Edward C. Matthews, Children's Hospital, Cincinnati 29, Ohio.

Dr. Maryethel Meyer, 1677 Wadsworth Ave., Lakewood, Colo.

Dr. Robert W. Niehaus, 2728 Erie Ave., Cincinnati 8, Ohio.

Dr. Everett A. Nitzke, 3718 Ingersoll Ave., Des Moines 12, Iowa.

Dr. Irving R. Ohren, 1930 W. Mitchell St., Milwaukee, Wis.

Dr. Thomas K. Oliver, Jr., Children's Hospital, Columbus 5, Ohio.

Dr. John Robert Patterson, 411 Nichols Rd., Kansas City, Mo.

Dr. Charles H. Patton, Jr., 11 McKeen St., Brunswick, Maine.
Dr. Shirley J. Peterson, 303 Grove St., Barrington, Ill.
Dr. Dalton T. Phillips, 10 Fillmore Place, White Plains, N. Y.
Dr. Bartlett Wilhite Ramsey, 10th Ave. & Fillmore St., Topeka, Kan.
Dr. Joseph Rivkin, 44 S. Gratiot, Mt. Clemens, Mich.
Dr. James R. Scheip, 375 East Town St., Columbus 15, Ohio.
Dr. Charles Scheuber, 237 Lang Rd., Ft. Sam Houston Village No. 2, San Antonio, Texas.
Dr. Robert W. Schroeder, 39 S. Main St., Fond du Lac, Wis.
Dr. Theodore D. Scurletis, 3700 Fifth Ave., Pittsburgh 3, Pa.
Dr. Howard Lee Seabright, Suite 1207, Medico-Dental Bldg., San Diego, Calif.
Dr. J. Randolph Sharpsteen, Jr., Man Memorial Hospital, Man, West Va.
Dr. Melville I. Singer, 13071 Belfast Dr., Garden Grove, Calif.
Dr. Fred Newman Smith, 1421 Camp Ave., Rockford, Ill.
Dr. Hugh Burns Spencer, 2828 E. 15th St., Tulsa, Okla.
Dr. Louis B. Sternberg, 107 Fairmeade Rd., Louisville 7, Ky.
Dr. Harry G. E. Stoeckle, Jr., 1208 Winnie, Galveston, Texas.
Dr. Grant Suttie, 2nd and Franklin Sts., DeKalb, Ill.
Dr. Edgar Chew Sweeney, 208 Doctors Bldg., Charlotte, N. C.
Dr. Norman S. Talner, Department of Pediatrics, University Hospital, Ann Arbor, Mich.
Dr. Paul M. Taylor, Jr., Magee Hospital, Pittsburgh 13, Pa.
Dr. Samuel M. Thomas, Apt. 48-F Lockbourne Manor, Lockbourne AFB, Columbus 17, Ohio.
Dr. David D. Thomasson, 1630 N. Jefferson, Springfield, Mo.
Dr. Arthur Lee Thompson, 6125 Scotten Ave., Detroit 10, Mich.
Dr. Mary Jean Tillou, 552 Linden Ave., East Aurora, N. Y.
Dr. Constance Vitanza, 102 Oak St., Binghamton, N. Y.
Dr. James Stark White, Jr., N. C. Memorial Hospital, Chapel Hill, N. C.
Dr. Robert J. Wirtshafter, 826 E. 61st St., Chicago 37, Ill.
Dr. Noel Catching Womack, Jr., 906 N. State St., Jackson, Miss.
Dr. Harold L. Wright, Jr., 2307 Parkwood, Ann Arbor, Mich.
Dr. F. Marshall Zahller, 5517 Military Ave., Omaha, Neb.
Dr. Kenneth Z. Zike, 4614 Sunset Blvd., Los Angeles 27, Calif.

*Special certificates—noncitizens:*

Dr. Filemon Tantoco Del Carmen, 4701 Old Sta. Mesa, Manila, Philippines.
Dr. Mohammad Bagher Hosseini, 54 Shields Place, N. Arlington, N. J.
Dr. Leonard S. James, Apt. 5-B, 780 Riverside Drive, Manhattan, N. Y.
Dr. Mehmet Burhanettin Say, Meharry Medical College, Nashville 8, Tenn.
Dr. Guillermo Tovar, Este 10, No. 248, Caracas, Venezuela.

The following pediatricians were certified in the subspecialty of Pediatric Allergy at the examination held in Chicago, Ill., on June 13, 1956:

Dr. Leo B. Burgin, 151 Kent, Brookline, Mass.
Dr. Claude A. Frazier, 516 City Bldg., Asheville, N. C.
Dr. John P. McGovern, 3509 Montrose Blvd., Houston, Texas.
Dr. Allen D. Shapiro, 202 Grand St., Newburgh, N. Y.

At an earlier examination, the following pediatricians were certified in Pediatric Allergy:

Dr. Vincent J. Fontana, 116 E. 53rd St., New York, N. Y.
Dr. Lewis J. Schloss, 170 E. 77th St., New York, N. Y.

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The **University of Minnesota** announces a continuation course in *Pediatrics for Pediatricians* to be held at the Center for Continuation Study from Sept. 25 to 27, 1956. This year's course will feature panel discussions of pediatric emergencies, endocrine disorders, heart diseases, allergic conditions, and behavior disorders as well as lectures on other pediatric topics of current interest. Dr. Francis Howell Wright, Professor and Head, Department of Pediatrics, University of Chicago Medical School, will be guest

speaker for the course, which will be presented under the direction of Dr. John A. Anderson, Professor and Head, Department of Pediatrics. All registrants are invited to attend the Irvine McQuarrie Lecture on Wednesday evening, September 26, and the annual scientific meeting of the Northwestern Pediatric Society at Bayport, Minnesota, on Friday, September 28. Lodging and meal accommodations are available at the Center for Continuation Study.

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The **New York Medical College-Flower and Fifth Avenue Hospitals** announce a postgraduate course in *Pediatric Allergy* under the direction of Dr. Bret Ratner, Nov. 7, 1956, to May 29, 1957, thirty sessions, Wednesdays 9 A.M. to 4 P.M. Applicants must be certified in pediatrics or have the requirements for certification. Enrollment limited. Apply: Office of the Dean, New York Medical College, Fifth Ave. at 106th St., New York 29, N. Y.

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Applications for the residency from July 1, 1957, to June 30, 1958, in *Pediatric Oncology* at **Memorial Center for Cancer and Allied Diseases** in New York will be received up to Nov. 1, 1956. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th St., New York 21, N. Y.

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The **Adolescent Unit at the Children's Hospital, Boston,** is now offering a general practice type of postgraduate training in the care of adolescents. One year traineeships are available to a few properly qualified physicians who have had two or more years of hospital experience following graduation from medical school. The teaching staff includes a gynecologist, endocrinologist, gastroenterologist, cardiologists, psychiatrists, etc., and is directed by Dr. J. R. Gallagher to whom any inquiries should be sent. A limited number of stipends are available.

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The Committee on the Fetus and Newborn Infant of the **American Academy of Pediatrics** has recently issued a statement concerning the use of oxygen in the treatment of the premature infant. It follows closely the action taken by many individual hospitals and some health departments. The statement is as follows:

The accumulated evidence definitely incriminates the excessive use of oxygen as a major factor in the cause of retrolental fibroplasia in premature infants. "Excessive use" implies concentrations of more than 40 per cent or the prolongation of administration after the indication for its use has passed. It is possible that even short periods of administration of higher concentration may be harmful.

On the other hand, the intelligent use of oxygen can be the means of saving the lives of hypoxic, dyspneic, and cyanotic babies. It would be unwise to arbitrarily deny adequate oxygen (and perhaps life) to those babies because of possible injury to the eyes of some.

Accordingly, the following recommendations are made:

1. Oxygen should be prescribed only on medical order the same as any drug or treatment. (Except in emergency.)

2. Oxygen should not be administered routinely but only upon specific medical indication.

3. Oxygen concentration should be kept at the lowest possible level that will relieve the symptoms for which it is given, if possible not over 40 per cent.

4. Oxygen therapy should be discontinued as soon as the indication for it has passed.

5. Ordinarily, the indications for supplemental oxygen are general cyanosis (not acrocyanosis) and dyspnea. The urgency of treating these symptoms must rest with the clinical judgment of the attending physician.

6. Oxygen concentration must be determined by means of an oxygen analyzer as often as necessary to keep it properly stabilized but at least every four hours.

7. A source which does not contain or deliver more than 40 per cent oxygen will insure against exceeding that concentration but may not be adequate in those occasional instances where higher concentration is desired. If such a restricted source of oxygen is employed, additional oxygen should be available for those special instances where it is indicated.

8. There are no apparent contraindications to the use of supplemental oxygen in infants weighing more than 5 pounds.

# Books

**Adrenal Functions in Infants and Children.** Lytt I. Gardner, M.D., ed., New York, 1956, Grune & Stratton. Price $6.75.

This book of 215 pages is an expanded version of the 102-page report of the Thirteenth Ross (M & R) Pediatric Research Conference entitled *Adrenal Function in Infants and Children.* The discussions particularly are more complete and apparently verbatim. The text reads remarkably well so that with a little imagination one feels as though he were really present during this most interesting symposium. Reading it will reward one with a wealth of important and provocative information.

Some of the more interesting observations were that full-term infants from 2 weeks to 10 months show a pattern of steroid excretion which is qualitatively different from that of adults. There is also a qualitative difference between urinary steroid excreted by premature infants and that of full-term infants. Most newborn infants respond to ACTH with blood levels of free corticoid similar to those of adults but a few do not and some have elevated levels even without ACTH or without experimental stress. A partial defect in synthesis of compound F is suggested by the data in adrenogenital syndrome; there is evidence of an enzymatic defect in hydroxylation at C-11. This may be the basis for the mechanism of hypertension in this syndrome and the reason why the hypertension responds so well to even small doses of cortisone. Patients with early rheumatic fever have definite evidence of adrenal insufficiency. However, they respond to ACTH with adequate levels of plasma steroids. Salicylate therapy does not bring the steroid levels to normal.

The Barr Skin Biopsy Test of Chromosomal Sex is described in the Appendix.

This more detailed report will be most useful, especially to pediatricians and endocrinologists. Such a symposium was needed to bring experts together in this fast-moving area of basic research and clinical application.

**Lues connata.** Doz. Dr. Johannes Oehme, Leipzig, 1956, Georg Thieme, 114 pages. Price DM 26.

A monograph on congenital syphilis based on the material observed in the Leipzig Children's Clinic from 1946 to 1954. The serology, diagnosis (with emphasis on roentgenology), prophylaxis, and treatment are discussed in different sections. The book is practical and stresses prevention by the treatment of the mother during pregnancy: "After treatment of the mother during pregnancy with at least 12 million units of penicillin we have never seen a child with lues connata."

**Foundations of Nutrition,** ed. 5. Clara M. Taylor, Ph.D., and Grace Macleod, Ph.D., New York, 1956, The Macmillan Co., 620 pages. Price $6.00.

This is a new edition of the text by the late Mary Swartz Rose which was first published in 1927. The authors, from the department of nutrition of Teachers College, Columbia University, have revised the text to include the many advances that have been made since 1944. Its purpose is a text on nutrition for college courses.

**The Office Assistant.** Portia M. Frederick and Carol Towner, Philadelphia, 1956, W. B. Saunders Co., 351 pages. Price $4.75.

A useful, practical book for assistants, secretaries, and receptionists who work in doctors' offices. It goes into the details of record keeping, telephone technique, bookkeeping, collections, instrument sterilization, supplies, and like matters which are so important if the office is to be run efficiently and smoothly. A good book for the office library.

**Health Observation of School Children,** ed. 2. George M. Wheatley, M.D., and Grace T. Hallock, New York, 1956, McGraw-Hill Book Co., 488 pages. Price $6.50.

A revised edition of the 1951 text. With the increasing tendency to utilize the teacher in the school health program, this text for teachers has found a definite field of usefulness.

# Editor's Column

## BED REST FOR FEVER

PROBABLY every practitioner who starts in by giving the time-honored direction to keep the child in bed as long as he has a "temperature" early in his practice encounters the harassed mother who looks him in the face and sarcastically replies, "I wish *you* would try to keep him in bed." Most practitioners learn that "quiet" rather than "bed rest" is usually sufficient and far more practical, and the direction changes to "keep him as quiet as you can." The soundness of this advice for the vast majority of the self-limited illnesses which plague the early years of childhood is confirmed by the unusual study of Gibson published in this issue. His report is of additional interest because the study was carried out by a busy practitioner on the material in his routine home and office practice. It demonstrates how the "enquiring mind" can contribute to medical knowledge as well as the wielder of the microscope and test tube.

## OSLER TOASTS JACOBI

OUR attention was recently called to a most delightful after-dinner talk by Osler on the occasion of a dinner held at Delmonico's in New York, May 5, 1900, honoring the seventieth anniversary of the birthday of Dr. Abraham Jacobi. Four hundred twenty-five of Dr. Jacobi's friends and professional colleagues were present and the list is a veritable "Who's Who" of prominent physicians and citizens at that time. One of the toasts was a poem by S. Weir Mitchell. Among the other toasts were one by Seth Low, president of Columbia "In Relation to Medical Education," and one by Carl Schurz, "The Citizen." Dr. Osler's toast was "The Scientist." The addresses, together with Dr. Jacobi's response, were privately printed in a volume for the subscribers to the dinner, and may be found in a few of the medical libraries. We are confident that many of our readers will enjoy Dr. Osler's remarks.

### "THE SCIENTIST"

ADDRESS OF DR. WILLIAM OSLER

Gibbon very wisely says that the only one person capable of passing a correct judgment upon the works of an individual is the author himself. Who knows so well as he the merit of the performance; who so interested in them? Fully agreeing, as every author should, with this authoritative statement, I must begin with an apology to Dr. Jacobi for an attempt to usurp his function, but under the circumstances he will forgive me.

A first and most surprising impression in a review of our friend's literary work is its very modest amount—only three or four volumes and some sixty

major monographs and essays. Knowing the encyclopedic character of the man, how commendable seems this moderation! The first publication against his name is the Bonn thesis, 1851, *"Cogitationes de Vita Rerum Naturálium."* I doubt if Dr. Jacobi could now appreciate the Cogitationes. The thesis, which is modest only in size, has all the dogmatic freshness of the production of a youth of one-and-twenty. The conclusion of the whole matter is given in a few brief lines at the close: *"Nil extra naturam, nil extra materiae leges,"* and there is a third and concluding phrase which I refrain from quoting. It is interesting to note so early in his career the influence of the great master, Rudolph Virchow, from whose writings several quotations are given. With one phrase I remember to have been caught years ago: *"Die Wissenschaften und der Glaube schliessen sich aus."* Science and faith have nothing to do with each other, and only worry comes from a neglect of that strong statement by Tennyson of their essential divergence:

"We have but Faith, we cannot know;
For Knowledge is of things we see."

Then comes the most impressive period in our author's life—silence for seven or eight years, during which I can find in indexes and catalogues nothing against either his name or his reputation. It is unique, almost, in the literary history of our profession. Would that this more than Pythagorean period of self-restraint could be emulated to-day! But think of the desolation to editors if all the graduates of all the schools of all these States thought and worked, but did not write for seven years after their graduation!

In this audience it seems almost superfluous to speak of the professional writings of Dr. Jacobi. Of his larger works the "Diphtheria" monograph and the "Treatise on the Therapeutics of Infancy and Childhood" have been guides and counselors to thousands of physicians all over the land. Nowhere has there been a better student of diphtheria or a sounder exponent of the subject than Abraham Jacobi. One of his earliest works, the contributions in connection with Dr. Noeggerath, I could not find. Dr Jacobi mentioned the other night in Washington that it had cost them about a thousand dollars to publish them. I understand that it has disappeared absolutely. It is not known whether Dr. Jacobi possesses copies, nor is it known how much it cost the authors to buy up the entire edition, which is the only possible explanation of its rarity.

Of the monographs and special articles, I should like to speak at length were there time, particularly of the splendid contributions upon the intestinal disorders of children. The monograph on the thymus gland is a model of careful research. You know as well as I of his scholarly and sound contributions in the various systems of medicine which have appeared from time to time. Of the many occasional addresses, that entitled *Non Nocere*, before the International Congress at Rome, and the appreciative sketch of Virchow, are models of their kind. I was much interested in one well-worn booklet in the Surgeon-General's Library—the earliest of his contributions in the collection of 1860 or 1861—in which a series of cases is narrated, and in which he gives a statement of how to teach the subject of pediatrics in

practical classes in the dispensaries. In this he was, I believe, a pioneer in the United States.

I come now to what may be considered the most important part of his life's work, that relating to infant-feeding. It may be said that the safety of a nation depends on the care of its infants, and no one in this country has done so much for their bodily welfare as Dr. Jacobi. Had they any other language but a cry, countless thousands of colic-stricken babes and sucklings would ordain great praise to him this evening. For more than thirty years we find this problem engaging his closest attention, and he has never tired of urging proper methods upon the profession and the public—methods which have always been characterized by his strong clear sense. There is no single question before this nation today of greater importance than how to return to natural methods in the nature of infants, and you will pardon me if I here make a slight digression. The neglect of the natural mode is an old story in Anglo-Saxondom. St. Augustine, so Bede tells us, wrote to Pope Gregory complaining that the question of infant-feeding was worrying him not a little. I understand that a systematic effort is to be made to supply to every child born in this land its rightful sustenance for one year at least. Under the auspices of the Pediatric Society and the Woman's Christian Temperance Union, a Woman's Infant-Suckling Union is to be established which will strive to make it a criminal offence against the State to bottle-feed any infant, and which will provide in large and well-equipped sucklingries ample sustenance when a mother from any cause is unable to do her duty. Roteh tells me that the action on the part of the Pediatric Society has been influenced by an exhaustive collective investigation on the future of bottle-fed babies, in which it is clearly shown that intellectual obliquity, moral perversion and special crankiness of all kinds result directly from the early warp given to the mind of the child by the gross and unworthy deception to which it is subjected—a deception which extends through many months of the most plastic period of its life.

According to these researches you can tell a bottle-fed man at a glance, or rather at a touch. *Feel the tip of his nose.* In all sucklings, the physical effects of breast pressure on the nose are not alone evidenced in the manner set forth so graphically by Mr. Shandy, but in addition the two cartilages are kept separate and do not join, whereas in bottle-fed babies, in whom there is no pressure on the tip of the nose, these structures rapidly unite, and, in the adult, present to the finger a single sharp outline, entirely different from the split, bifid condition in the breast-fed child. The collective investigation demonstrates that all silver democrats, many populists, and the cranks of all descriptions have been bottle-fed, and show the characteristic nose tip. Utopian as the scheme may appear (and directly suggested, of course, by Plato), who can question the enormous benefits which would follow the substitution of such sucklingries for the present Walker-Gordon Laboratories and other devices—benefits untold to helpless infants; blessings to thousands upon thousands of women whose energies would be directed into their natural lactiferous channels, and, more important still, a

gradual elimination of those pernicious bottle-fed influences, to which may be attributed so many evils both to the State and to the individual.

Looking over Dr. Jacobi's books and papers, one gets the impression of an honesty of purpose and a sincerity in them all. There is no clap-trap, no gallery-play, but a faithful administration of an intellectual trust, and, what is more, the professional spirit is reflected in them always on the nobler side. There is a double meaning in the well-known line:

"Heard melodies are sweet, but those unheard are sweeter."

And let us hope that what may come from his pen in the future may excel his past performances. A volume of poems, "*Songs in Silence*," written *in der Stille* of his prison-house, would be most acceptable, or a novel (of which Dr. Janeway has just spoken to me) in three volumes, or, better than either, his "Jugenderinnerungen," which he really should leave to us as an evening legacy.

To speak seriously, this magnificent demonstration is a tribute not less to Dr. Jacobi's personal worth than to the uniform and consistent character of his professional career. The things which should, do not always accompany old age. The honor, love, obedience and troops of friends are not for all of us as the shadows lengthen. Too many, unfortunately, find themselves at seventy "nursing a dwindling faculty of joy," amid an alien generation. Fed on other intellectual food, trained by other rules than those in vogue, they are too often, as Matthew Arnold describes Empedocles, "in ceaseless opposition." Against this interstitial decay, which insidiously, with no pace perceived, steals over us, there is but one antiseptic, one protection, the cultivation and retention of a sense of professional responsibility. Happiness at threescore years and ten is for the man who has learned to adjust his mental processes to the changing condition of the time. In all of us senility begins at forty—forty sharp—sometimes earlier. To obviate the inevitable tendency, a tendency which ends in intellectual staleness as surely as in bodily weakness, a man must not live in his own generation. He must keep fresh by keeping in contact with fresh young minds, and ever retain a keen receptiveness to the ideas of those who follow him. Our dear friend has fortunately been able to do this in a remarkable manner, since he is one

"Whose ever-balanced soul
Business could not make dull, nor passion wild,
Who saw life steadily and saw it whole."